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(54) Prodrugs of phosphonates

Wirkstoffvorläufer von Phosphonaten

Pro-médicaments dérivés de phosphonates

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• Bronson, Joanne J.
Madison, CT 06443 (US)

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(74) Representative:
Kinzebach, Werner, Dr. et al
Patentanwälte
Reitstötter, Kinzebach und Partner
Postfach 86 06 49
81633 München (DE)

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EP-A- 0 205 826 EP-A- 0 269 947
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(73) Proprietors:

- INSTITUTE OF ORGANIC CHEMISTRY AND BIOCHEMISTRY
OF THE ACADEMY OF SCIENCES OF THE CZECH REPUBLIC
166 10 Praha 6 (CZ)
- Rega Stichting Vzw.
B- 3000 Leuven (BE)

- CHEMICAL ABSTRACTS vol. 112, no. 19, 7 May 1990, abstract no. 179685h, Columbus, Ohio, US; A. HOLY et al.: 'Synthesis of N-(2-Phosphonylmethoxyethyl) Derivatives of Heterocyclic Bases'
- CHEMICAL ABSTRACTS vol. 108, no. 21, 23 May 1988, abstract no. 179636k, Columbus, Ohio, US; E. DE CLERCQ et al.: 'Antiviral Activity of Phosphonylmetaxaikyl Derivatives of Purines and Pyrimidines'

(72) Inventors:

- Starrett, John Edward, Jr.
Middletown, CT 06457 (US)
- Mansuri, Muzammil M.
Cheshire, CT 06410 (US)
- Martin, John C.
Cheshire, CT 06410 (US)
- Tortolani, David R.
Meriden, CT 06450 (US)

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Description

The present invention relates to orally active prodrugs of phosphonate nucleotide analogs, their pharmaceutically acceptable acid addition salts, a process for their production, and to their use. The prodrugs of the present invention exhibit antitumor activity and a broad spectrum of antiviral activity.

Infectious viral diseases are recognized as an important medical problem. Progress against infectious viral diseases requires the development of drugs with selective antiviral activity while remaining benign to normal cell lines. Among the antiviral agents currently under study, which seem to possess selectivity, are phosphonate nucleotide analogs. In general, these compounds are structural analogs of the monophosphates nucleoside analogs.

A number of phosphonate nucleoside analogs have been described in the literature. These nucleoside analogs have been described as potent and selective antiviral agents with activity against a broad spectrum of DNA and RNA viruses.

For example, 9-(3-hydroxy-2-phosphonylmethoxypropyl (HPMP) and (2-phosphonylmethoxy)ethyl (PME) analogs of purine (adenine (A), guanine (G), 2,6-diaminopurine (DAP), 2-monoaminopurine (MAP), hypoxanthine (Hx) and pyrimidine (cytosine (C), uracil (U), thymine (T) were evaluated for antiviral properties. (S)-HPMPA, (S)-cyclic HPMPA, (S)-HPMPC, (S)-HPMPG, (S)-HPMPDAP, PMEDAP, PMEG and PMEA were active against herpes simplex virus, type 1 and 2 (HSV-1 and -2). (S)-HPMPA and (S)-cyclic HPMPA were active against varicella zoster virus (VZV). (S)-HPMPC was active against human cytomegalovirus (HCMV), a common cause of opportunistic infection in AIDS patients. (S)-HPMPA and (S)-cyclic HPMPA are active against adenovirus and vaccinia virus. PMEA, PMEDAP, and PMEMAP are active against human immunodeficiency virus (HIV), the human retrovirus responsible for AIDS. De Clercq, et al., Antiviral Research, 8: 261-272 (1987).

Bronson, et al., report on the series of acyclic nucleotide analogs having a common PME side chain attached to a purine or pyrimidine base which were prepared and selected for in vivo antiviral activity against retroviruses and herpes viruses. The adenine analog, PMEA, showed good in vitro activity against HIV and Rauscher murine leukemia virus (R-MuLV), and was more potent in vivo than 3'-azido-3'-deoxythymidine (AZT) in the treatment of R-MuLV in mice. PMEA also had a significant antiviral effect in vivo against murine cytomegalovirus (MCMV), and in vitro activity against HCMV. The guanine analog, PMEG, was exceptionally potent in vitro against herpes viruses. In vivo, PMEG was >50-fold more potent than acyclovir against HSV 1 infection in mice. Nucleotide Analogs as Antiviral Agents; ACS Symposium Series 401; Martin, J. C. Ed.: Washington, DC, 1989, Chapter 5, pp. 72-87. Kim, et al., in J. Med. Chem., 33: 1207-1213 (1990), describe a similar series of compounds.

De Clercq, et al., in Nature, 323: 464-467 (1986) state that (S)-HPMPA has potent and selective activity against a broad spectrum of DNA viruses, including HSV-1 and 2, VZV, thymidine kinase-deficient (TK⁻) mutants of herpes simplex HCMV, phocid herpesvirus type 1 (seal herpesvirus, SeHV), the simian herpesvirus platyrhinae (HVP), suid herpesvirus type 1 (SHV-1, or pseudorabies virus or Aujeszky's disease virus), bovid herpesvirus type 1 (infectious bovine rhinotracheitis virus, BHV-1), equid herpesvirus type 1 (equine abortion virus, EHV-1), African swine fever (ASF) virus, vaccinia virus; and human adenoviruses, and retroviruses such as murine sarcoma virus (MSV). It is also reported that, in mice and rabbits in vivo, the compound is effective against both local and systemic infections with herpes simplex virus type 1, including herpetic keratitis caused by a TK⁻ mutant which is resistant to the classical anti-herpes drugs.

European Patent Application 205,826, to De Clercq, et al., published Dec. 30, 1986, discloses that HPMPA analogs are active against Moloney mouse sarcoma virus, and are expected to be effective against retroviruses in general. Reist and Sturm in PCT/U.S. 84/00737, published December 6, 1984 disclosed new phosphonic acid analogs of nucleoside phosphates which are useful as antivirals for incorporation into viral DNA.

Adenine phosphonic acid analogs and their synthesis are disclosed in the United Kingdom Patent application of Holy, et al., GB 2,134,907A, published on August 22, 1984, and its related United States Patent, No. 4,659,825. A preferred example of one of these compounds, is known as (S)-9-((3-hydroxy-2-phosphonylmethoxy)propyl)adenine (HPMPA). HPMPA was disclosed by E. DeClercq, et al., in Nature, 323: 464-467, (1986), in Antiviral Research, 8: 261-272, (1987), and earlier by A. Holy, et al., Nucleic Acids Research, Symposium Series No. 14: 277-278, (1984).

Phosphonylmethoxyalkylpurine analogs have also been evaluated for their antitumor activity in murine tumor models. HPMPA, PMEA, and PMEG were found to be active against intraperitoneal P388 leukemia. PMEG was also found to be active against B16 melanoma. Rose, et al., J. of the Natl. Cancer Inst., Vol. 82, No. 6 (1990).

A problem with nucleotides and other ionic organophosphate esters is their inability to traverse biological membranes. Liebman, et al., J. Biol. Chem., 216: 823 (1955); Roll et al., J. Biol. Chem., 220: 439 (1956). These compounds must, therefore, be given parenterally in order to achieve adequate serum levels to exert an antiviral effect.

Parenteral treatment is highly undesirable, especially with HIV infected patients. With HIV infected patients oral treatment is preferred since (i) HIV infected patients are very ill and need to be on chronic chemotherapy programs to maintain their health; (ii) the risk of using needle stick and presence of blood is high for health workers; (iii) disposal of infected needles is problem; and (iv) the need for long-term maintenance therapy.

The inventors of this invention have carried out studies in order to circumvent the above-mentioned problem. The

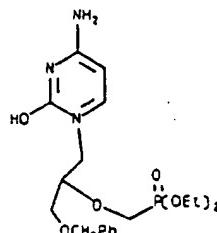
present application, thus, relates to the preparation and use of a number of oral prodrugs of phosphonate nucleotide analogs.

In J. Med. Chem., 32:1457-1463 (1989), Bronson *et al.*, disclose the synthesis of HPMPC wherein the following compound is disclosed as an intermediate

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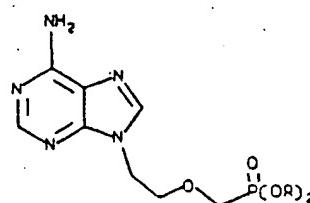
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In Nucleotide Analogs as Antiviral Agents, ACS Symposium Series 401, J.C. Martin, Ed., p. 72, American Chemical Society, Washington, D.C. (1989), Bronson *et al.*, disclose the synthesis of phosphorylmethoxy ether derivatives 20 wherein the following compound was disclosed as an intermediate

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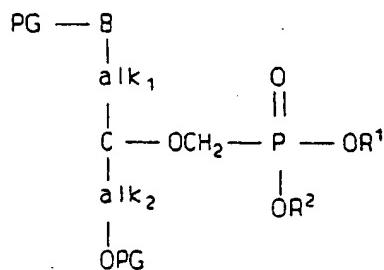


wherein R is ethyl or isopropyl.

European Patent Application EP-270,885 of Webb, *et al.*, published June 15, 1988 discloses a process for the preparation of purin-9-ylalkylenoxymethyl phosphonic acids, wherein several intermediates are produced in the practice of 35 the process. One such intermediate is dialkylphosphorylmethyl which has the general structural formula

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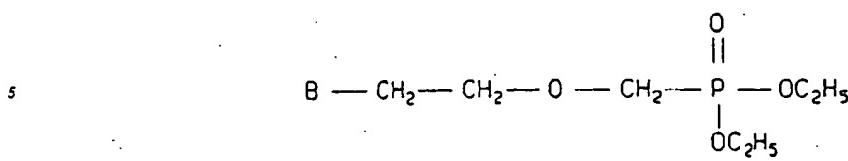
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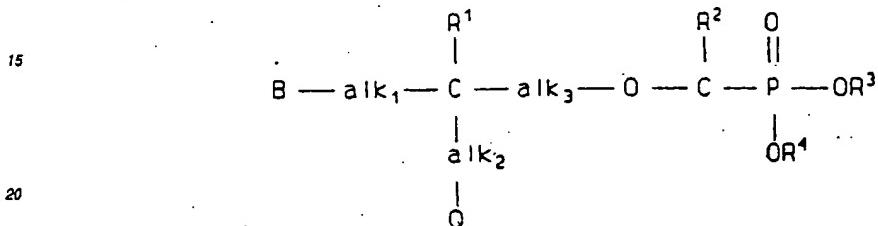
wherein R¹ and R², independently, are selected from C₁₋₆ alkyl.

50 European Patent Application EP 253,412 of Holy, *et al.*, published January 20, 1988, discloses the preparation of a series of N-phosphorylmethoxyalkyl derivatives of pyrimidine and purine bases exhibiting antiviral activity, wherein in the practice of the process, several intermediates are produced. One such intermediate has the general structural formula

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10 European Patent Application EP-269,947 of R. R. Webb, II, et al., published on June 8, 1988, discloses a series antiviral agents which are phosphonomethoxyalkylene purine and pyrimidine derivatives having the following general structure

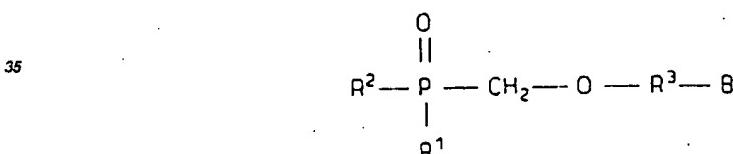


wherein R³ and R⁴ are independently selected from hydrogen, C₁₋₁₆ alkyl, phenyl and phenyl-C₁₋₄-alkylene.

25 The art compounds are generally distinguished from the compounds of the instant invention by the nature of the groups attached to the phosphorous atom. There is no disclosure or suggestion in the above references, or combination thereof, which would make obvious the use of a suitably protected phosphonate derivative prodrug for oral use.

This invention relates to prodrugs of phosphonate nucleotide analogs which exhibit antitumor activity and a broad spectrum of antiviral activity and some of which may be used orally.

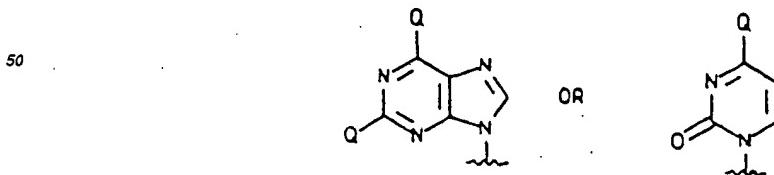
30 The compounds of the instant invention comprise a diester-phosphonate link to nucleoside analogs of pyrimidine and purine bases. More particularly, it relates to compounds of the general structural formula as shown in Formula I



FORMULA I

wherein

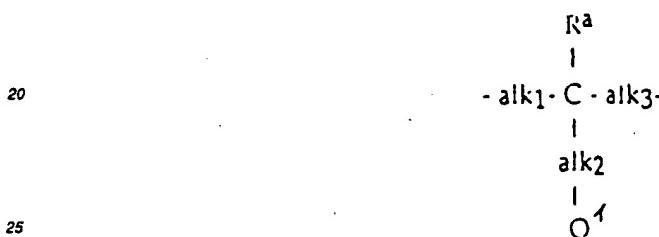
45 B represents adenine (A), cytosine (C), guanine (G), thymine (T), uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx),



wherein

Q is independently chosen from H, Cl, NHR⁵, NR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH or NCHN(R⁵)₂;

- * R¹ and R² are identical or different and independently of one another are each OR⁴, NH₂, NHR⁵ or N(R⁵)₂; R¹ and R² optionally being linked with each other to form a cyclic group, or R¹ or R² optionally being linked to R³ to form a cyclic group;
- 5 R³ represents C₁-C₂₀ alkylene which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen; or R³ is CH(CH₂OR⁶)CH₂, whereby R¹ and R² each independently may additionally represent OH, and R⁶ is a hydrolyzable ester group;
- 10 R⁴ represents a physiologically hydrolyzable ester group selected from CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R, S, or RS stereochemistry), CH₂C(P⁵)₂CH₂OH, or CH₂OR⁵; or R⁴ represents C₄-C₂₀ alkyl, aryl-alkyl or aryl which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen provided that R¹ and R² are not simultaneously alkoxy;
- 15 R⁵ represents C₁-C₂₀ alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy and halogen; provided that those compounds of the above formula I are excluded wherein B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil, R³ is



30 wherein alk₁ is bonded to B, alk₁, alk₂ and alk₃ are independently selected from a chemical bond or C₁-C₄ alkylene, R^a is hydrogen or C₁-C₄ alkyl and Q¹ is hydrogen or hydroxyl, and R¹ and R² are unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy.

Included within the scope of the invention are the pharmaceutically acceptable acid addition salts, the metal salts and the solvate of the compounds of Formula I which may exist in various tautomeric forms.

35 In one aspect, the application relates to a process for the preparation of the compounds of Formula I.

In another aspect, the application relates to the use of the compounds of Formula I as a method for the treatment of viral infections in a mammal, which comprises administering an effective non-toxic dose of at least one compound of Formula I.

Another aspect of the application relates to the use of the compounds of Formula I as a method for inhibiting growth of a tumor in a mammal bearing a tumor which comprises administering an effective non-toxic dose of at least one compound of Formula I.

The compounds of Formula I are prodrugs of phosphonate nucleotides and have the same utility as the known or parent nucleotide analog. Thus the compounds of Formula I are useful as antiviral and antitumor agents.

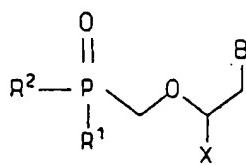
The compounds of the present invention provide marked advantages over known nucleotides or analogs thereof in that these compounds are orally active.

45 The most preferred compounds of the invention are listed below, and experimental details for their preparation and characterization follow. Those which are not shown by specific example are readily prepared by analogous procedures.

A preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula (II):

50

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FORMULA III

10

wherein

15 B, R¹ and R² are as described in Formula I, provided that when Q is NCHN(R⁵)₂, then R⁵ is not CH₃; X represents hydrogen, CH₂OR⁶ (R;S; or RS stereochemistry), or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH₂OR⁶, R¹ and R², may additionally be independently chosen from OH; and R⁶ is a hydrolyzable ester group.

20 Another preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula (III):



FORMULA III

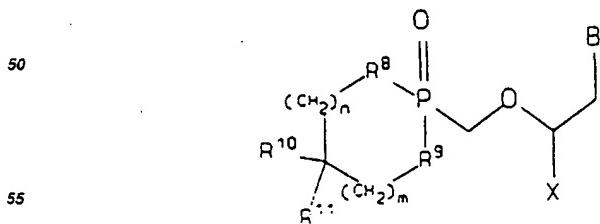
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wherein

35 B, and R¹ are as previously described in Formula I; X represents hydrogen, CH₂OR⁶ (R;S; or RS stereochemistry) or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH₂OR⁶, R¹ may additionally be OH; and R⁶ is a hydrolyzable ester group; R⁷ represents OH, NH₂, NHR⁵, or NR⁵₂; and

40 R⁵ is as described in Formula I, provided that those compounds of the above formula III are excluded wherein B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil, X is alk₂-Q₁ wherein alk₂ selected from a chemical bond or C₁-C₄ alkylene, Q₁ is hydrogen or hydroxyl, and R¹ and R⁷ are OH, unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy.

45 Still another preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula (IV):



FORMULA IV

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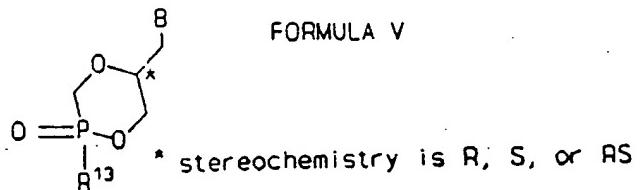
wherein

- R⁸ and R⁹ are identical or different and independently of one another are each NR¹², or oxygen;
 R¹⁰ and R¹¹ are identical or different and independently of one another are each hydrogen, or R⁵;
 R¹² represents hydrogen or a lower alkyl;
 m and n are identical or different and independently of one another are each 0 or 1;
 5 B and R⁵ are as described in Formula I; and
 X is as described in Formula II.

Yet another preferred example of the compounds of the instant invention are the compounds having the general structural formula as shown in Formula V

10

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20 wherein

- R¹³ represents OR⁴, NHR⁵, NR⁵₂, or OH, provided that R¹³ is not OH when B is A or C; and
 B, R⁴ and R⁵ are as described in Formula I.
- 25 The term "C₁ to C₂₀ alkyl" as used herein and in the claims (unless the context indicates otherwise) means saturated or unsaturated, branched or straight chain hydrocarbon group having 1 to 20 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, etc. Unless otherwise specified in the particular instance, the term "substituted or unsubstituted" as used herein and in the claims is intended to mean hydrocarbon group wherein an atom, element or group is regarded as having replaced a hydrogen atom, said substituted alkyl groups are preferably substituted with
 30 a member selected from the group consisting of hydroxy and halogen.

The term "prodrug" as used herein and in the claims (unless the context indicates otherwise) denotes a derivative of an active drug which is converted after administration back to the active drug. More particularly, it refers to derivatives of nucleotide phosphonates antiviral drugs which are capable of undergoing hydrolysis of the ester moiety or oxidative cleavage of the ester or amide moiety so as to release active, free drug. The physiologically hydrolyzable groups serve
 35 as prodrugs by being hydrolyzed in the body to yield the parent drug per se, and thus, the prodrugs of the present invention are preferably administered orally.

Synthesis of the phosphonate nucleotide analogs

- 40 The phosphonate nucleotide analogs are known compounds and therefore, the compounds as such and their chemical synthesis are not a part of the present invention. The synthesis of a number of phosphonate nucleotide analogs have been described in the literature.

For example, the synthesis of the phosphonates PMEA is disclosed in Holy and Rosenberg, *Collect. Czech. Chem. Commun.*, 52:2801, (1987), and Bronson, et al, *Nucleotide Analogues as Antiviral Agents*, ACS Symposium Series 45 401, J.C. Martin, Ed., p. 72, American Chemical Society, Washington, D.C. (1989).

Bronson, et al, *J. Med. Chem.*, 32: 1457-1463 (1989) discloses the preparation of HPMPC from (R)-2,3-O-isopropylideneglycerol.

European Patent Application 253,412, published January 20, 1988 to Holy, et al, discloses methods for the preparation of PME and HPMP analogs of pyrimidine and purine bases.

- 50 Recently Holy et al *Collect. Czech. Chem. Commun.*, 54: 2190-2210 (1989), described the preparation of N-(2-phosphonylmethoxy-ethyl) ("PME") analogs of purine and pyrimidine bases, as analogs of the antiviral 9-(2-phosphonylmethoxyethyl)adenine ("PMEA"). The synthesis consists of alkylation of alkali metal salts of heterocyclic bases or their N- or O-substituted analogs with diethyl 2-p-toluenesulfonyloxyethoxyethylphosphonate, 2-chloroethoxyethylphosphonate, or 2-bromoethoxyethyl-phosphonate. The obtained N-(2-diethoxyphosphonylmethoxyethyl) analogs of heterocyclic bases were treated with bromotrimethylsilane to give phosphonic acids. The phosphonic acids were prepared from pyrimidines (uracil, cytosine and their 5-methyl analogs), purines (adenine and its N⁶ and C(2)-substituted analogs, hypoxanthine, guanine, 6-hydrazinopurine and 6-methylthiopurine etc.) and their analogs (3-deazaadenine etc.).

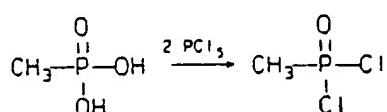
• The synthesis of HPMPA is disclosed in Holy, Rosenberg, and Dvorakova, Collect. Czech. Chem. Commun. 54:2190 (1989).

Synthesis of dialkyl phosphonates

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Quast, et al, Synthesis 490 (1974), has shown that dichlorophosphonates can be prepared by reacting phosphonates with PCl_5 :

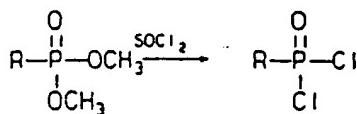
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Moedritzer, K. CA 82, 86340, has shown that dichlorophosphonates can be prepared by reacting dimethylphosphonates with thionyl chloride.

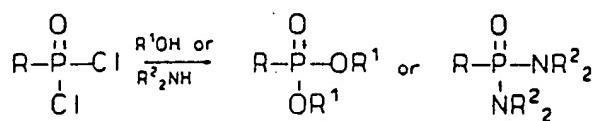
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Stowell, et al, (Tetrahedron Lett., 3261, (1990)) has shown that dichlorophosphonates can be reacted with alcohols or amines to give dialkylesters or dialkylamides:

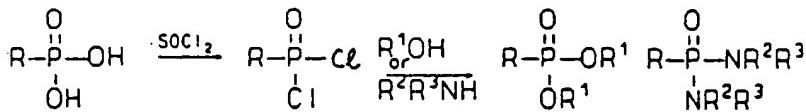
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The substituted phosphonates of the present invention were prepared by several methods: 1) Reaction of the phosphonate with thionyl chloride to give the dichlorophosphonate which was reacted further to give the disubstituted phosphonate:

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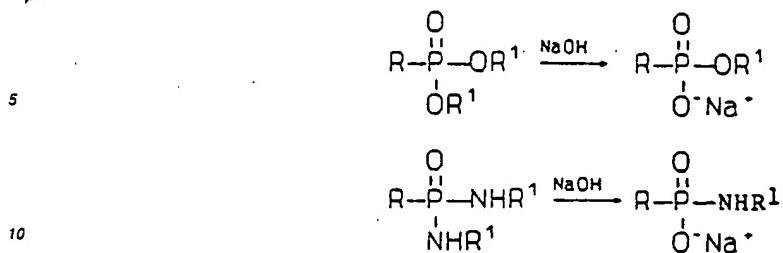


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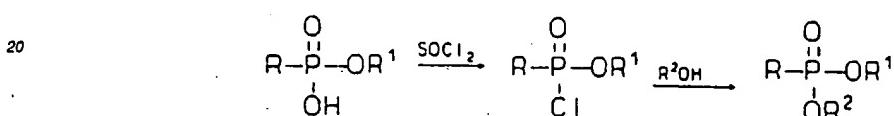
2) Mono substituted phosphonates were obtained by the basic hydrolysis of the disubstituted phosphonate:

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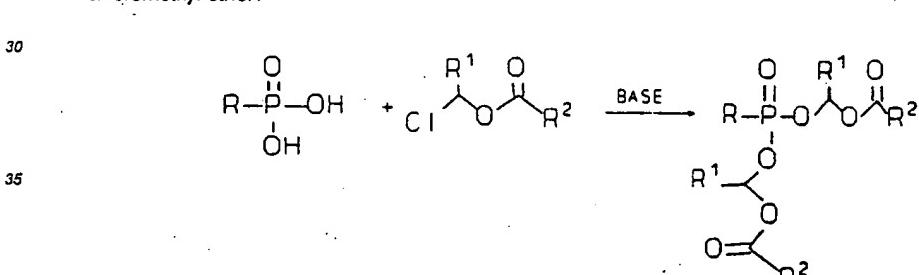
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15 3) The monosubstituted phosphonates were chlorinated as before and reacted with a different alcohol or amine to give variably substituted phosphonates:



4) Diacyloxyalkyl phosphonates were obtained by reaction of the unsubstituted phosphonate with a substituted



PROTOCOL FOR DETERMINING ORAL BIOAVAILABILITY OF PRODRUGS

Groups of rats, 3 rats per group were given a single iv dose of 30 mg/kg of PMEA or a single oral dose of 30 mg-equiv/kg of PMEA or PMEA prodrug. Urine was collected in 0-24 hr and 24-48 hr intervals and analyzed for concentration of PMEA. The bioavailability of PMEA based on urinary excretion data and the bioavailability of PMEA when given as a prodrug was determined. The results are summarized below.

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ORAL BIOAVAILABILITY OF SELECTED PMEA PRODRUGS IN RATS		
	COMPOUND OF EXAM- PLE NO.	ABSOLUTE BIOAVAILA- BILITY
10	1 (PMEA)	7.8
	8	17.0
15	11	15.4
	12	14.6
	13	34.9**
	14	6.5
	15	14.2
20	21	16.2
	31	14.0
	32	11.1

**DETECTED AS THE MONOETHYL ESTER

25

30

IN VITRO ACTIVITY OF SELECTED PMEA PRODRUGS AGAINST HSV-2 (G STRAIN)			
	COMPOUND OF EXAM- PLE NO.	ID ₅₀ (μg/mL) ^a	TOXICITY (μg/mL)
35	1 (PMEA)	39	>166
	8	0.28	100
	11	0.17	100
	12	<0.1	100
40	13	3.3	100
	14	8.1	100
	15	>100	100
45	21	110	>166
	31	42	>166
	32	34	>166

^aDOSE WHICH GIVES A 50 % REDUCTION OF PLACQUE FORMATION

50

The compounds of Formula I may be formulated for oral or parenteral use in a conventional manner using known pharmaceutical carriers and excipients, and they may be presented in unit dosage form or in multiple dose containers. The compositions may be in the form of tablets, capsules, solutions, suspensions or emulsions. These compounds may also be formulated as suppositories utilizing conventional suppository bases such as cocoa butter or other fatty materials. The compounds may, if desired, be administered in combination with other antiviral antibiotics.

When provided in unit dosage forms, the compositions may contain from about 0.1 to about 100 mg/kg/dose of the active ingredient of Formula I. The dosage of the compounds of Formula I is dependent on such factors as the weight

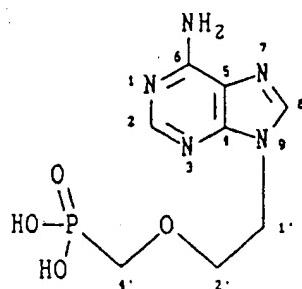
and age of the patient, as well as the particular nature and severity of the disease, and within the discretion of the physician. The dosage for adult human treatment may vary depending on the frequency and route of administration.

The following examples are intended for illustrative purpose only and are not to be construed as limiting the invention in sphere or scope. All temperatures are understood to be in degrees in C when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. Except where otherwise noted, ^1H spectra were recorded at 300 MHz and ^{13}C spectra were recorded at 75 MHz. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. NMR assignments are based on the numbering system shown below:

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The nature of the shifts as to multiplicity is reported as broad singlets (bs), singlets (s), multiplet (m), doublet (d), doublet of doublets (dd), triplet (t), or quartet (q). Coupling constants are given in hertz. When not specified, abbreviations employed are standard American Chemical Society (ACS) abbreviations as entered on the ACS Style Guide. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. All compounds gave satisfactory elemental analyses, or high resolution mass spectrometry (HRMS).

30 I. GENERAL EXPERIMENTAL METHODS FOR COMPOUNDS LISTED IN TABLE I:

The compounds listed in Table I were synthesized by the corresponding method given at the end of the table. The reaction time, temperature and yield are given in Table I. The structure of the examples corresponds to either Figure 1 or Figure 2 given at the top of Table I. Spectral data for all compounds are given in the Examples which follow.

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TABLE I. STRUCTURES AND EXPERIMENTAL DATA FOR PMEA PRODRUGS

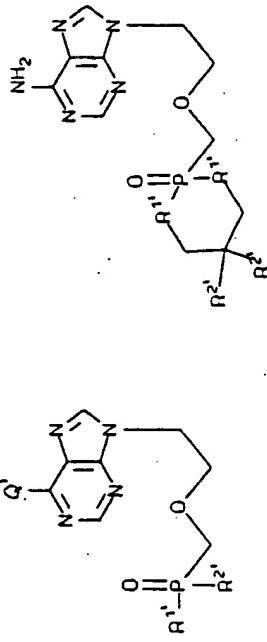


FIGURE 1 FIGURE 2

Example No.	Fig	R1'	R2'	Q'	EXPERIMENTAL		
					Method	Temp°C	Time(h)
2	1	iPrO	-R'	NH ₂	e		4
3	1	iPrO	HO	OH	e		

Example No.	Rg	R1'	R2'	Q'	EXPERIMENTAL			
					Method	Temp°C	Time(h)	Yield %
4	1	iPro	-R'	C1	e			
5	1	iPro	-R'	H	e			
8	1	t-BuC(O)OCH ₂ O	-R'	NH ₂	e	-		
9	1	t-BuC(O)OCH ₂ O	iPro	NH ₂	e			
10	1	(CH ₃) ₃ N(+) (CH ₂) ₂ O	O'	NH ₂	e	-		
11	1	EtC(O)OCH ₂ O	-R'	NH ₂	e			
12	1	iPrC(O)OCH ₂ O	-R'	NH ₂	e			
13	1	iPrC(O)OCH ₂ O	CH ₃ CH ₂ O	NH ₂	e			
14	1	tBuC(O)OCH ₂ O	OH	NH ₂	e			
15	1	iPro	PhO	NH ₂	e			

EXPERIMENTAL								
Example No.	Pig	R1'	R2'	Q'	Method	Temp°C	Time(h)	Yield %
16	1	t-BuC(O)OCH ₂ O	Et ₂ Nc(O)CH ₂ O	NH ₂	e			
17	2	O	H	NH ₂	C*	22	16	
18	1	Et ₂ N	=R'	NH ₂	C	22	16	18
19	1	iPRO	O'	NH ₂	B	60	24	75
20	2	O	CH ₃	NH ₂	C	40	24	56
21	1	HO(CH ₂) ₃ O	O'	NH ₂	B	60	2	50
22	1	CH ₃ (CH ₂)PO	HO	NH ₂	E	70	16	29
23	1	H ₂ NCH ₂ C(CH ₃) ₂ CH ₂ NH-	HO	NH ₂	B	60	1.5	61

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Example No.	Fig	R ¹	R ²	Q ¹	EXPERIMENTAL		
					Method	Temp °C	Time(h)
24	1	HOCH ₂ C(CH ₃) ₂ CH ₂ O	HO	NH ₂	D	60	1.5
25	2	NH	CH ₃	NH ₂	C	40	24
26	2	NCH ₃	H	NH ₂	F	82	24
27	1	Et ₂ NC(O)CH ₂ O	O'	NH ₂	F,D,d	0;22	20;0.3
28	1	HOC(O)CH ₂ O	HO	NH ₂	D	22	0.1
29	1	BuOC(O)CH ₂ O	=R ¹	NH ₂	F	82	1
30	1	EtoC(O)CH ₂ O	=R ¹	NH ₂	F	82	2
31	1	PhO	O'	NH ₂	D	22	1
32	1	PhO	=R ¹	NH ₂	F	22	20
33	1	iPr ₂ NC(O)CH ₂ O	O ⁻	NH ₂	F,D,d	22;22	0.8;0.3

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Example No.	Fig	STRUCTURE	R1'	R2'	Q'	EXPERIMENTAL			
						Method	Temp°C	Time(h)	Yield %
34	1	pNO ₂ PhCH ₂ O		-R ¹	NH ₂	F	82	1	15
35	1	pNO ₂ PhCH ₂ O		O'	NH ₂	D	60	20	78
36	1	CCl ₃ CH ₂ O		-R ¹	NH ₂	F	82	20	44
37	1	CCl ₃ CH ₂ O		HO	NH ₂	D	60	1	69
38	1	PhC(O)OCH ₂ O		-R ¹	NH ₂	E	22	20	9
39	1	pCF ₃ PhCH ₂ O		-R ¹	NH ₂	F	82	3	15
40	1	HOCH ₂ C(F ₂)CH ₂ O		HO	NH ₂	F;D ^{a,d}	82;22	1;1	18
41	1	pCF ₃ PhCH ₂ O		HO	NH ₂	D	60	20	82
42	1	CH ₃ (CH ₂) ₃ NH		-R ¹	NH ₂	F	82	20	27
43	1	(CH ₃) ₂ CHCH ₂ O		-R ¹	NH ₂	A	60	3	75

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EXPERIMENTAL					
Example No.	Fig	R1'	R2'	Q'	Method
			=R ¹	NH ₂	Temp °C
44	1	(CH ₃) ₂ CH(CH ₂) ₂ O		A	80
					1.5
					77

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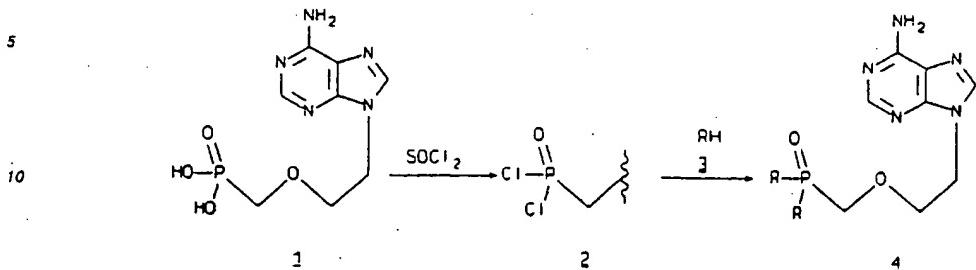
- The crude product obtained from method F was employed directly in method D. Temperature and time are given for methods F and D, respectively.
- The impure product obtained from column chromatography was recrystallized from 25% MeOH/CH₃CN.
- The impure product obtained from column chromatography was recrystallized from CH₃CN.
- See detailed experimental section for synthesis of hydroxyacetamides and difluoroalcohol.
- Where no method is given, see detailed experimental section for specific examples.

METHOD OF SYNTHESIS FOR THE COMPOUNDS OF TABLE 1

A: A suspension of 1.00 g (3.66 mmol) of PMEA (1) in 50 mL of thionyl chloride was refluxed for 1 h (see eq. 1). The homogeneous, orange-red solution was cooled and the solvents were removed in vacuo to afford crude dichlorophosphonate 2. The dichloride was taken up in alcohol or amine 3 and stirred at the temperature and the time

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given in Table I. After cooling the reaction to room temperature the solvents were removed in vacuo. The residue was purified on a 30 mm flash chromatography column, eluting with 10% MeOH/CH₂Cl₂ to afford 4. (See eq. 1)



- and washed with water. The filtrate was cooled to 0 °C and the resulting solid was collected and washed with cold water. The solids were combined and dried overnight at 0.005 mm to afford 106 mg (0.23 mmol) of monooctyl-PMEA.
- 5 F: This reaction was performed similarly to method A, except crude dichlorophosphonate 2 was suspended in 30 mL of acetonitrile before adding alcohol or amine 3 (see equation 1).

SPECIFIC EXPERIMENTAL METHODS FOR COMPOUNDS LISTED IN TABLE I.

10 EXAMPLE 1

Synthesis of 9-(2-Phosphonylmethoxy)ethyladenine (PMEA).

A solution of PMEA diisopropyl ester (75.5 g, 0.21 mol) in 800 mL of anhydrous acetonitrile was treated with bromotrimethylsilane (258 g, 1.69 mol). The resulting clear, yellow solution was stirred at room temperature under argon for about 16 hours. The reaction mixture was concentrated in vacuo and the yellow residue was placed under high vacuum for about 5 hours. 400 mL of water was added next, causing immediate formation of a white precipitate. 500 mL of acetone was added and the pale yellow slurry was stirred at room temperature for about 14 hours. The solid was collected by filtration, washing twice with 150 mL of acetone and once with 150 mL of anhydrous ether. An additional portion of solid was collected from the filtrate to provide a total of 55.0 g (90%) of PMEA as an off-white crystalline solid.

20 m.p.> 250°C; UV_{max} (H₂O) 208 nm (ϵ = 19,600) 260 nm (ϵ = 14,100); UV_{max} (0.1 N HCl) 210 nm (ϵ = 19,000) 260NM (ϵ = 13,700); UV_{max} (0.1 N NaOH) 216 nm (ϵ = 9,600) 262 nm (ϵ = 14,500); ¹H NMR (DMSO-d₆) δ 8.14 (s, 1 H), 8.13 (s, 1 H), 7.27 (br s, 2 H, NH₂), 4.32 (t, J = 5, 2 H, H-1'), 3.87 (t, J = 5, 2H, H-2'), 3.59 (d, J = 9, 2H, H-4'); ¹³C NMR (DMSO-d₆) δ 151.10 (c-6), 148.70 (C-2), 146.28 (C-4), 143.80 (C-8), 118.05 (C-5), 69.94 (d, J =10, C-2'), 66.27 (d, J =160, C-4'), 43.15 (C-1').

EXAMPLE 2

Synthesis of PMEA, di-(isopropyl ester).

A slurry of adenine (21.2 g, 157 mmol), 2-[(diisopropylphosphonyl)methoxy]ethyl methanesulfonate (50.0 g, 157 mmol, prepared according to the procedure described by J.J. Bronson et al, in *J. Med. Chem.*, **32**: 1457, (1989)), and cesium carbonate (56.0 g, 173 mmol) in 160 mL of anhydrous DMF was heated to 120°C in a 3-necked, 500-mL, round-bottomed flask equipped with a mechanical stirrer and argon inlet adapter. The reaction mixture was stirred at 120°C for about 5 hours and then was allowed to cool to room temperature. Insoluble material was removed by filtration and the filtrate was concentrated in vacuo to give 66 g of a yellow solid. Purification by column chromatography on silica gel (10:1, elute with 3% to 5% to 7% MeOH/CH₂Cl₂) provided 33 g of an off-white solid. Recrystallization from ethyl acetate provided 30.1 g (54%) of PMEA, diisopropyl ester as a white solid.

40 Mp 136-138°C; UV_{max} (MeOH) 262 nm (ϵ = 14,360); ¹H NMR (DMSO-d₆) δ 8.15 (s, 1H), 8.09 (s, 1H), 7.21 (br s, exch, 2H, NH₂), 4.50 (apparent octet, J = 6.5 H, 2H, 2POCH), 4.34 (t, J = 5 H, 2H, NCH₂), 3.91 (t, J = 5 Hz, 2H, CH₂OCH₂P), 3.79 (d, J = 8 Hz, 2H, OCH₂P), 1.18 (d, J = 6.5 H, 6H, POCH(CH₃)₂), and 1.13 (d, J = 6.5 Hz, 6H, POCH(CH₃)₂); ¹³C NMR (DMSO-d₆) δ 155.86 (C-6), 152.23 (C-2), 149.46 (C-4), 140.90 (C-8), 118.57 (C-5), 70.22 (d, J = 10 Hz, POCH), 70.05 (d, J = 12 Hz, (CH₂OCH₂P), 64.50 (d, J = 165 Hz, OCH₂P), 42.35 (NCH₂), 23.61 [d, J = 7 H, POCH(CH₃)₂], and 23.52 [d, J = 7 Hz, POCH(CH₃)₂]; mass spectrum (methane DCI), m/e (rel intensity) 358 (MH⁺, 100), 344 (10), 316 (10).

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Anal. Calc. for C ₁₄ H ₂₄ N ₅ O ₄ P:	C, 47.06;	H, 6.77;	N, 19.60.
Found:	C, 47.06;	H, 7.04;	N, 19.65.

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EXAMPLE 3

Synthesis of 9-(2-Phosphonylmethoxy)ethylhypoxanthine (PMEHx), mono-(isopropyl ester).

5 A solution of 6-chloro-9-(2-phosphonylmethoxy)ethylpurine, diisopropyl ester (1g, 2.65 mmol) in 27 mL of 1 N NaOH was heated at reflux for 1 h, cooled to room temperature, acidified to pH 1 with 1 N HCl and concentrated in vacuo. The residue was purified by C-18 silica gel column chromatography, eluting with 20% MeOH/H₂O to afford 0.51 g (68%) of the title compound.

10 Mp 192-194°C. ¹H NMR (d₆-DMSO) 12.27 (1H, br s, NH), 8.04, 8.02 (2H, 2s, H-2, H-8), 4.39 (1H, septet, J=6, CH(CH₃)₂), 4.30 (2H, t, J=5, H-1'), 3.85 (2H, t, J=5, H-2'), 3.65 (2H, d, J=8.5, H-4'), 1.10 (6H, d, J=6, CH₃). ¹³C NMR (D₂O) 157.57 (C=O), 149.94, 149.72 (C-2, C-4), 143.02 (C-8), 119.94 (C-5), 72.09 (CH(CH₃)₂, d, J=6), 71.70 (C-2', d, J=13), 67.80 (C-4', d, J=160), 47.05 (C-1'), 25.28 (CH₃, d, J=4). IR (KBr) 3423, 2979, 1716, 1642, 1587, 1562. MS (FAB) 317 (M+H, 100).

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Anal. Calcd for C ₁₁ H ₁₇ N ₄ O ₅ P · 0.4 H ₂ O:	C, 40.95;	H, 5.53;	N, 17.37.
Found:	C, 41.19;	H, 5.68;	N, 17.51.

EXAMPLE 4

Synthesis of 6-Chloro-9-(2-Phosphonylmethoxy)ethylpurine, di-(isopropyl ester).

25 To a rapidly stirred solution of 9.86 g (63.8 mmol) of 6-chloropurine in 350 mL of anhydrous DMF was added 1.91 g (63.8 mmol) of sodium hydride (80% in mineral oil). The heterogeneous mixture was heated at 95 °C for about 20 hours, cooled to room temperature and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 5% MeOH/CH₂Cl₂ to give 4.53 g of the title compound.

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30 ¹H NMR (d₆-DMSO) 8.76 (1H, s, H-8), 8.63 (1H, s, H-2), 4.82 (2H, t, J=5, H-1'), 4.42 (2H, septet, J=6, CH(CH₃)₂), 3.93 (2H, t, J=5, H-2'), 3.75 (2H, d, J=8, H-4'), 1.11 (6H, d, J=6, CH₃), 1.05 (6H, d, J=6, CH₃). ¹³C NMR (d₆-DMSO) 152.44 (C-6), 151.88 (C-2), 149.39 (C-4), 148.13 (C-8), 131.13 (C-5), 70.24 (CH(CH₃)₂, d, J=6), 70.00 (C-2', d, J=11), 64.64 (C-4', d, J=165), 43.43 (C-1'), 23.65 (CH₃, d, J=4.5), 23.47 (CH₃, d, J=4.5). IR (KBr) 3459, 3077, 2982, 2936, 1564. MS (methane/DCI) 377 (M+H, 100).

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Anal. Calcd for C ₁₄ H ₂₂ N ₄ O ₄ Cl ₁ P ₁ :	C, 44.63;	H, 5.89;	N, 14.87.
Found:	C, 44.40;	H, 5.93;	N, 14.53.

EXAMPLE 5

Synthesis of 9-(2-phosphonylmethoxy)ethylpurine, di-(isopropyl ester).

45 A solution of 6-Chloro-9-(2-phosphonylmethoxy)ethylpurine, diisopropyl ester (0.94 g, 2.5 mmol) in 20 mL of ethanol/cyclohexene (1:1) was treated with 0.5 g of Pd(OH)₂/C. The reaction was stirred at reflux for about 20 hours, diluted with hot ethanol and filtered through celite. The filtrate was concentrated in vacuo and the residue was purified 50 by flash column chromatography, eluting with 10% MeOH/CH₂Cl₂ to afford 0.49 g (58%) of the title purine as a clear yellow oil.

55 ¹H NMR (d₆-DMSO) 9.14, 8.92, 8.55 (3H, 3s, H-2, H-6, H-8), 4.47 (2H, t, J=5, H-1'), 4.42 (2H, septet, J=6, CH(CH₃)₂), 3.94 (2H, t, J=5, H-2'), 3.77 (2H, d, J=8, H-4'), 1.12 (6H, d, J=6, CH₃), 1.05 (6H, d, J=6, CH₃). IR 3459, 2982, 2937, 1597, 1581, 1506. MS (methane/DCI) 343 (M+H, 100), 329 (12), 301 (50).

5	Anal. Calcd for C ₁₄ H ₂₃ N ₄ O ₄ P • 0.25 H ₂ O:	C, 48.50;	H, 6.83;	N, 16.16.
	Found:	C, 48.55;	H, 6.71;	N, 15.88.

EXAMPLE 6

10 Synthesis of hydroxyacetamides necessary for preparation of Example 20 and Example 24.

(a) 2-hydroxy-N,N-diethylacetamide

15 A solution of 10.5 g (0.0702 mol) of 2-chloro-N,N-diethylacetamide in 35 mL of glacial acetic acid was refluxed for about 16 hours. The solvents were removed in vacuo, the last traces of acetic acid being azeotropically removed with toluene. The residue was dissolved in 125 mL of methanol and treated with 10.85 g (0.20 mol) of sodium methoxide. The reaction was stirred for about 3 hours and neutralized with Dowex 50X8-200 acidic ion exchange resin. The solvents were removed in vacuo and the residue was purified on a flash chromatography column, eluting with hexane/ethyl acetate 1:1 to give 6.75 g (73%) of 2-hydroxy-N,N-diethylacetamide.

20 (b) 2-hydroxy-N,N-diisopropylacetamide

25 To a solution of 44.5 g (0.44 mol) of N,N-diisopropyl amine in 125 mL of hexane cooled to -78 °C was added dropwise 17.6 mL (0.22 mol) of chloroacetyl chloride. After completion of the addition, the cooling bath was removed and stirring was continued for about 30 minutes. The isopropylammonium chloride was removed by filtration through celite and the filtrate was stripped to give 30.5 g (77%) of 2-chloro-N,N-diisopropylacetamide. Hydrolysis of this compound as described above afforded a 45% yield of 2-hydroxy-N,N-diisopropylacetamide.

EXAMPLE 7

30 Synthesis of the difluoroalcohol necessary for the preparation of Example 31.

(a) 2,2-Difluoro-3-hydroxy-propan-1-ol

35 A solution of 9.07 g (0.0521 mol) of 1,3-diacyl acetone in 20 mL of DAST was stirred at 22 °C for 2 days, diluted with ethyl acetate, washed with saturated NaHCO₃ and water, then dried over Na₂SO₄ and concentrated to yield 9.54 g of 1,3-diacyl-2,2-difluoropropane. The diacyl-difluoropropane (7.53 g, 38.4 mmol) was dissolved in 300 mL of methanol and treated with 6.45 g (119 mmol) of sodium methoxide. After stirring at 22 °C for about 2.5 hours, the reaction was neutralized with Dowex 50X8-200 acidic ion exchange resin, filtered and stripped to give 3.7 g (86%) of the title compound.

EXAMPLE 8

Synthesis of PMEA, di-(pivaloyloxymethyl ester)

45 To a rapidly stirred solution of 1.00 g (3.66 mmol) of PMEA in 15 ml of anhydrous DMF was added 2.08 g (7.32 mmol) of N,N'-dicyclohexyl-4-morpholine carboxamidine and 2.75 g (18.33 mmol) of chloromethyl pivalate. The heterogeneous mixture became homogeneous after about 15 minutes and was then allowed to stir at 22°C for about 36 hours. The insolubles were filtered off and the filtrate was concentrated in vacuo. The residue was then partitioned between (50 ml) water and (50 ml) toluene, separated and the water layer was then extracted with (2 x 50 ml) toluene. The toluene layers were combined and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 5% MeOH/CH₂Cl₂ to give 0.59 g (32%) of the title compound.

55 ¹H NMR(CDCl₃) 8.32(1H, s, H-8), 7.91(1H, s, H-2), 5.77(2H, s, NH₂), 5.63(4H, m, CH₂OP), 4.37(2H, t, J=5.0, H-1'), 3.92 (2H,t,J=5.0,H-2'), 3.82 (2H, d, J=7.7, H-4'), 1.18(18H, s, CH₃). ¹³C NMR (CDCl₃) 177.55(C=O), 156.23(C-6), 153.45(C-2), 150.48(C-4), 142.05(C-8), 119.85(C-5), 82.04 (CH₂OP,d,J=6.0), 71.70(C-2', d, J=9.8), 65.86(C-4', d, J=167), 43.63(C-1'), 38.95(CC(=O), 27.11(CH₃). IR(KBr) 3366, 3178, 2976, 1754, 1660, 1600. MS(Isobutane/DCI) 502(M+H, 100).

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Anal. Calcd. for C ₂₀ H ₃₂ N ₅ O ₈ P ₁ :	C, 47.90;	H, 6.43;	N, 13.96.
Found:	C, 48.02;	H, 6.27;	N, 13.63.

EXAMPLE 9

10 Synthesis of PMEA, (mono-isopropyl, mono-pivaloyloxymethyl) ester

To a rapidly stirred solution of 200 mg (0.6 mmol) of monoisopropyl PMEA (example 11) in 5 ml of anhydrous DMF was added 0.83 ml (6.0 mmol) of Et₃N and 0.45 g (3.0 mmol) of chloromethylpivalate. The heterogeneous mixture became homogeneous after addition of Et₃N and was then allowed to stir at 22°C for about 3 days. The mixture was concentrated in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH₂Cl₂ to give 190 mg (74%) of the title compound.

20 ¹H NMR(CDCl₃) 8.30(1H, s, H-8), 7.91(1H, s, H-2), 5.94(2H, s, NH₂), 5.57(2H, d, J=12.5, CH₂OP), 4.73 (1H, septet, J=6.2, CH), 4.36(2H, t, J=5.0, H-1), 3.90(2H, t, J=5.0, H-2'), 3.75(2H, d, J=8.0, H-4'), 1.25(6H, d, J=6.2, CH₃), 1.17(9H, s, CH₃). ¹³C NMR (CDCl₃) 177(C=O), 155.51(C-6), 152.91(C-2), 149.8 (C-4), 141.43(C-8), 119.36(C-5), 81.90(CH₂OP, d, J=5.6), 72.18(CHOP, d, J=7.0), 71.19(C-2', d, J=10.0), 65.78(C-4', d, J=167), 43.37 (C-1), 38.68((CH₃)₃C), 26.84((CH₃)₃C), 23.92(CH₃CH, d, J=7), 23.85(CH₃CH, d, J=7). IR(KBr) 3432, 1754, 1668, 1602. MS(FAB) 430(M+H, 100).

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Anal. Calcd. for C ₁₇ H ₂₈ N ₅ O ₆ P ₁ • 0.50 H ₂ O:	C, 46.56;	H, 6.66;	N, 15.98.
Found:	C, 46.50;	H, 6.61;	N, 15.81.

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EXAMPLE 10

Synthesis of PMEA, mono-(choline ester)

35 A suspension of 2.00 g (7.33 mmol) of PMEA in 30 ml of thionyl chloride was refluxed for about 1 hour. The homogeneous, orange-red solution was cooled and the solvents were removed in vacuo to afford crude dichlorophosphonate. The dichloride was taken up in 40 ml of acetonitrile and then treated with 2.00 g (32.34 mmol) of anhydrous ethylene glycol at reflux for about 16 hours. After cooling to 22°C, the solvents were removed in vacuo. The residue was purified by silica gel chromatography, eluting with MeOH/CH₂Cl₂/NH₄OH 30/70/1 to give 1.42 g (65%) of mono(chloroethyl)ester.

40 A suspension of 460 mg (1.37 mmol) of the above compound in 30 ml of MeOH was saturated with Me₃N gas at 0°C. The reaction mixture was then sealed in a metal bomb and heated at 65°C for about 2 days.

After cooling the reaction to 22°C, the solvents were removed in vacuo and the residue was purified by C-18 chromatography, eluting with 15% MeOH/H₂O to give 270 mg (35% from PMEA) of the title compound.

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45 ¹H NMR(CD₃OD) 8.24(1H, s, H-8), 8.20(1H, s, H-2), 4.42(2H, t, J=5.0, H-1'), 4.12(2H, CH₂CH₂OP), 3.89(2H, t, J=5.0, H-2'), 3.64(2H,d,J=9.0,H-4'), 3.47 (2H, m, CH₂OP), 3.14(9H, s, CH₃). ¹³C NMR (CD₃OD) 157.55(C-6), 154.03(C-2), 151.02(C-4), 144.02(C-8), 120.15(C-5), 72.04(C-2'), 68.24(C-4',d, J=159), 68.05 (CH₂OP), 60.10(CH₂CH₂OP,d,J=4.9), 55.02(CH₃), 54.98(CH₃), 54.92(CH₃), 44.95(C-1'). IR(KBr) 3396, 1648, 1602, 1480. MS(FAB) 359(M+H,30).

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Anal. Calcd. for C ₁₃ H ₂₃ N ₆ O ₄ P ₁ • 2.5H ₂ O:	C, 38.60;	H, 7.00;	N, 20.78.
Found:	C, 38.26;	H, 6.60;	N, 20.47.

EXAMPLE 11

Synthesis of PMEA, di-(propionyloxymethyl ester)

5 To a rapidly stirred solution of 1.00 g (3.66 mmol) of PMEA in 15 ml of anhydrous DMF was added 2.08 g (7.32 mmol) of N,N'-dicyclohexyl-4-morpholine carboxamidine and 2.23 g (18.3 mmol) of chloromethylpropionate. The heterogeneous mixture became homogeneous within 30 minutes and was then allowed to stir at 22°C for about 5 days. The insolubles were filtered off and the filtrate was concentrated in vacuo. The residue was purified twice by silica gel chromatography (200:1), eluting with 5%MeOH/CH₂Cl₂ to give 0.14g (9%) of the title compound.

10 ¹H NMR(CDCl₃) 8.29(1H, s, H-8), 7.88(1H, s, H-2), 5.65(2H, s, NH₂), 5.60(4H, m, CH₂OP), 4.35(2H, t, J=5.0, H-1'), 3.89(2H, t, J=5.0, H-2'), 3.80(2H, d, J=7.8, H-4'), 2.34(4H, q, J=7.5 CH₃CH₂), 1.10 (6H, t, J=7.5, CH₃). IR(KBr) 3290, 3122, 1766, 1666, 1602. MS(FAB) 446(M+H, 100).

15

Anal. Calcd. for C ₁₆ H ₂₄ N ₅ O ₈ P ₁ :	C, 43.15;	H, 5.43;	N, 15.72.
Found:	C, 43.07;	H, 5.46;	N, 15.42.

20

EXAMPLE 12

Synthesis of PMEA, di-(isobutyryloxymethyl ester)

25 To a rapidly stirred solution of 1.00 g (3.66 mmol) of PMEA in 15 ml of anhydrous DMF was added 2.08 g (7.32 mmol) of N,N'-dicyclohexyl-4-morpholine carboxamidine and 2.48 g (18.3 mmol) of chloromethylisobutyrate. The heterogeneous mixture became homogeneous within 30 minutes and was then allowed to stir at 22°C for 5 days. The mixture was concentrated in vacuo, partitioned between (50 ml) water and (50 ml)toluene. The aqueous layer was extracted with (250 ml) toluene and the combined organic layer was concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 5% MeOH/CH₂Cl₂ to give 0.16 g (9%) of the title compound.

30 ¹H NMR(CDCl₃) 8.31(1H, s, H-8), 8.28(1H, s, H-2), 5.68(2H, s, NH₂), 5.59(4H, m, CH₂OP), 4.33(2H, t, J=5.0, H-1'), 3.88(2H, t, J=5.0, H-2'), 3.78(2H, d, J=7.7H, H-4'), 2.52(2H, apparent heptet, J=7.0, CH), 1.11(6H, d, J=7.0, CH₃). IR(KBr) 3360, 2980, 1758, 1660, 1602. MS(isobutane/DCI) 474(M+H, 100).

35

Anal. Calcd. for C ₁₈ H ₂₈ N ₅ O ₈ P ₁ • 0.65 H ₂ O:	C, 44.56;	H, 6.09;	N, 14.44.
Found:	C, 45.67;	H, 5.96;	N, 14.79.

40

EXAMPLE 13 (for comparison)

Synthesis of PMEA, (mono-ethyl, mono-isobutyryloxymethyl) ester

45 To a rapidly stirred solution of 400 mg (1.33 mmol) of monoethyl PMEA in 15 ml of anhydrous DMF was added 2.00 ml (14.3 mmol) of Et₃N and 1.0 g (6.7 mmol) of chloromethylpivalate. The heterogeneous mixture became homogeneous after addition of Et₃N and was then allowed to stir at 22°C for 2 days. The mixture was concentrated in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH₂Cl₂ to give 180 mg (33%) of the title compound.

50 ¹H NMR(CDCl₃) 8.32(1H, s, H-8), 7.92(1H, s, H-2), 5.74(2H, s, NH₂), 5.62(2H, m, OCH₂OP), 4.38 (2H, t, J=5.0, H-1'), 4.10(2H, m, CH₃CH₂OP), 3.92(2H, t, J=5.0, H-2'), 3.79(2H, d, J=8.0, H-4'), 1.27 (3H, t, J=7.0, CH₃CH₂), 1.18 (9H, s, ((CH₃)₂C). ¹³C NMR (CDCl₃) 176.87(C=O), 155.40(C-6), 152.94(C-2), 149.8(C-4), 141.51(C-8), 119.7(C-5), 81.85(CH₂OP, d, J=6.2), 71.26(C-2', d, J=10.2), 65.46(C-4', d, J=16.7), 62.73(CH₂CH₃, d, J=7.0), 43.49(C-1'), 38.70((CH₃)₃O), 26.84((CH₃)₃C), 16.27(CH₂CH₃, d, J=5.8). IR(KBr) 3288, 3120, 2982, 1752, 1666, 1600. MS(FAB) 416(M+H, 100).

5	Anal. Calcd. for C ₁₆ H ₂₆ N ₅ O ₆ P ₁ · 0.5H ₂ O: Found:	C, 45.28; C, 45.47;	H, 6.41; H, 6.34;	N, 16.51. N, 16.55.
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EXAMPLE 14

10 Synthesis of PMEA, mono-(pivaloyloxyethyl ester)

To a solution of sodium hydride(0.95 g, 80%, 31.7 mmol) and benzylalcohol (6.8 ml, 63.5 mmol) in anhydrous DMSO (50 ml) was added with stirring a solution of PMEA, diphenyl ester (3.4 g, 8 mmol, example 26) in DMSO(50 ml). The mixture was allowed to stir at 22°C for 1 h and concentrated to a volume of approximately 25 ml. EtOAc (200 mL) was added and the precipitate was collected by vacuum filtration. The precipitate was purified by C-18 chromatography, eluting with 20% MeOH/H₂O to give 2.09 g (68%) of PMEA, monobenzylester, sodium salt.

15 To 600 mg (1.56 mmoles) of the above compound in 14 ml of anhydrous DMF was added 2.16 ml (15.5 mmoles) of Et₃N and 1.44 g (9.61 mmol) of chloromethylpivalate. The mixture was allowed to stir at 22°C for 2 days, concentrated in vacuo and the resulting residue was used crude in the following step.

20 To a stirred solution of the crude mixed ester (300 mg) in 17 ml of EtOH and 17 ml of H₂O was added 3.45 ml of cyclohexene and 0.225g of 20% Pd(OH)₂/C. The mixture was heated at reflux for 1h, concentrated in vacuo and the residue purified by C-18 chromatography, eluting with 100% H₂O to give 270 mg (31% from PMEA, diphenyl ester) of the title compound.

25 ¹H NMR(d₆-DMSO) 8.09(2H, s, H-8, H-2), 7.17(2H, s, NH₂), 5.44(2H, m, CH₂OP), 4.26(2H, t, J=5.0, H-1'), 3.83 (2H,t, J=5.0, H-2'), 3.47(2H, d, J=8.0, H-4'), 1.04(9H, s, CH₃). ¹³C NMR (d₆-DMSO) 176.70(C=O), 155.98(C-6), 152.39(C-2), 149.55(C-4), 141.30(C-8), 118.59(C-5), 83.14(CH₂OP), 69.89(C-2'), 64.5(C-4'), 42.84 (C-1'), 38.13 ((CH₃)₃Q) 26.69(CH₃). IR(KBr) 3360, 1742, 1648, 1602.

MS(FAB) 386(M-H, 100). HRMS:

30

Calculated:	388.1386.
Found:	388.1377.

EXAMPLE 15

40 Synthesis of PMEA, (mono-isopropyl, mono-phenyl) ester

A suspension of 0.75 g (2.1 mmol) of monophenyl PMEA in 20 ml of thionyl chloride was refluxed for 1 h. The homogeneous, orange-red solution was cooled and the solvents were removed in vacuo to afford crude monochlorophosphonate. The residue was taken up in 40 ml of isopropyl alcohol and stirred for 16 h at 22°C. The solvents were removed in vacuo and the residue was purified by silica gel chromatography, eluting with 10% MeOH/CH₂Cl₂ to give 45 0.24g (29%) of the title compound.

Mp 96-99°C. ¹H NMR(CDCl₃) 8.31(1H, s, H-8), 7.87(1H, s, H-2), 7.19(5H, m, Ph), 5.96(2H, s, NH₂), 4.80 (1H, apparent heptet, J=6.2, CH), 4.36(2H, t, J=5.0, H-1'), 3.93(2H, t, J=5.0, H-2'), 3.86(2H, d, J=7.9, H-4'), 1.26(3H, d, J=6.2, CH₃), 1.21(3H, d, J=6.2 CH₃). ¹³C NMR (CDCl₃) 155.52(C-6), 152.88(C-2), 150.13(ArC, d, J=8.3), 149.89(C-4), 141.46(C-8), 129.71(ArC), 125.14(ArC), 120.50(ArC, d, J=4.5), 119.43(C-5), 72.65(CH, d, J=7.3), 71.18(C-2', d, J=10.6), 65.27(C-4', d, J=167.5), 43.45(C-1), 23.93(CH₃, d, J=4.5), 23.82(CH₃, d, J=4.5). IR(KBr) 3290, 3116, 1670, 1600. MS(Isobutane/DCI) 392(M+H, 100).

55

Anal. Calcd. for C ₁₇ H ₂₂ N ₅ O ₄ P ₁ :	C, 52.17;	H, 5.66;	N, 17.89.
Found:	C, 52.01;	H, 5.57;	N, 17.64.

EXAMPLE 16

Synthesis of PMEA, (mono-N,N-diethylacetamide, mono-pivaloyloxymethyl) ester

5 To a suspension of 0.100 g (0.239 mmol) of PMEA, mono-N,N-diethylacetamide ester (sodium salt) (Example 24) in 2.5 mL of CH₃CN was added 0.25 mL of Et₃N, whereupon the reaction became homogeneous. To this mixture was added 0.17 mL (1.19 mmol) of chloromethyl pivalate. The reaction was stirred at 22°C for 24h, evaporated to dryness in vacuo, and purified on a 20 mm flash column. The title compound eluted with 10 % MeOH/CH₂Cl₂ to give 25 mg (21%) of a colorless oil.

10 ¹H NMR (CDCl₃) 8.25 (1H, s, H-8), 7.94 (1H, s, H-2), 6.26 (2H, s, NH₂), 5.65 (1H, dd, J=12.3, 5.4, OCH₂O), 5.60 (1H, dd, J=12.3, 4.8, OCH₂O), 4.75 (1H, dd, J=14.7, 10.8, OCH₂C(O)), 4.56 (1H, dd, J=14.5, 14.3, OCH₂C(O)), 4.32 (2H, dd, J=5.7, 4.4, H-1), 3.97 (2H, d, J=8.4, H-4'), 3.91 (2H, t, J=4.8, H-2'), 3.28 (2H, q, J=7.5, CH₂CH₃), 3.09 (1H, q, J=7.2, CH₂CH₃), 1.12 (9H, s, (CH₃)₃). 1.07 (3H, m, CH₃CH₂), 1.05, (3H, t, J=6.9, CH₃CH₂). ¹³C NMR (CDCl₃) 177.85 (C(O)O), 166.25 (C(O)N), 156.34 (C-6), 153.48 (C-2), 150.49 (C-4), 142.22 (C-8), 119.79 (C-5), 81.94 ((CH₃)₃Q), 81.71 (OCH₂O), 71.55 (C-2', d, J=10), 65.10 (C-4', d, J=165), 63.99 (CQH₂OP), 43.53 (C-1'), 41.03 (NCH₂), 40.78 (NCH₂), 27.00 ((CH₃)₃), 14.21 (CH₃CH₂), 13.00 (CH₃CH₂). MS (FAB) 501 (M+H, 100). IR 3500-3000, 2978, 1750, 1654, 1600, 1480, 1250.

20

Anal. Calcd for: C ₂₀ H ₃₃ N ₆ O ₇ P · 0.5 H ₂ O	C, 47.15;	H, 6.72;	N, 16.50.
Found:	C, 47.30;	H, 6.58;	N, 16.14.

25

The following examples were prepared by the methods given in Table I.

EXAMPLE 17

PMEA, cyclic propanyldiester

30 Mp 195-199°C. ¹H NMR (d₆-DMSO) 8.13 (1H, s, H-8), 8.12 (1H, s, H-2), 4.35 (2H, t, J=4.8, H-1), 4.2 (4H, m, CH₂OP), 3.95 (2H, d, J=8.8, H-4'); 3.86 (2H, t, J=4.8, H-2'), 1.98 (1H, m, CH₂CH₂CH₂), 1.55 (1H, m, CH₂CH₂CH₂). ¹³C NMR (d₆-DMSO) 156.01 (C-6), 152.48 (C-2), 149.69 (C-4), 141.11 (C-8), 118.68 (C-5), 70.71 (C-2', d, J=13.8), 68.30 (CH₂OP, d, J=6.9), 64.55 (C-4', d, J=158), 42.52 (C-1'), 25.85 (CH₂CH₂CH₂, d, J=9.0). IR (KBr) 3351, 3169, 1660, 1601, 1256, 1063. MS (FAB) 314 (M+H, 100).

40

Anal. Calcd for: C ₁₁ H ₁₆ N ₅ O ₄ P · 1.5 H ₂ O	C, 38.85;	H, 5.63;	N, 20.60.
Found:	C, 38.63;	H, 5.46;	N, 20.49.

EXAMPLE 18

45

PMEA, bis-diethylamide

50 Mp 93-96°C. ¹H NMR (d₆-DMSO) 8.11 (1H, s, H-8), 8.07 (1H, s, H-2), 7.18 (2H, s, NH₂), 4.31 (2H, t, J=4.8, H-1), 3.85 (2H, t, J=4.8, H-2'), 3.68 (2H, d, J=8.1, H-4'), 2.70 (8H, m, CH₃CH₂), 0.86 (12H, t, J=7.0, CH₃). ¹³C NMR (d₆-DMSO) 155.98 (C-6), 152.33 (C-2), 149.63 (C-4), 141.04 (C-8), 118.75 (C-5), 70.30 (C-2', d, J=13.0), 66.30 (C-4', d, J=133), 42.63 (C-1'), 37.53 (CH₃CH₂), d, J=4.1), 13.93 (CH₃, d, J=1.9). IR (KBr) 3370-2935, 2875, 1680, 1649, 1605, 1211. MS (FAB) 384 (M+H, 100).

55

Anal. Calcd for: C ₁₆ H ₃₀ N ₇ O ₂ P · 0.5 H ₂ O	C, 48.96;	H, 7.96;	N, 24.99.
Found:	C, 48.85;	H, 7.77;	N, 24.92.

EXAMPLE 19

PMEA, mono-(isopropyl ester) (sodium salt)

5 Mp 77-85°C turned to glass and melted over next 40°C. ^1H NMR (d_6 -DMSO) 8.19 (1H, s, H-8), 8.13 (1H, s, H-2),
 7.22 (2H, s, NH₂), 4.30 (2H, t, J=4.4, H-1'), 4.10 (1H, m, OCH), 3.76 (2H, t, J=4.4, H-2'), 3.31 (2H, d, J=8.6, H-4'),
 0.90 (6H, d, J=6.0, CH₃). ^{13}C (d_6 -DMSO; 90 MHz), 155.90 (C-6), 152.35 (C-2), 149.54 (C-4), 141.39 (C-8), 118.53
 (C-5), 70.23 (OCH, d, J=10), 68.70 (C-4', d, J=192), 65.55 (C-2', d, J=5), 42.72 (C-1'), 24.43 (CH₃). IR (Film) 3321,
 3163, 1647, 1601, 1578. MS (FAB) 338 (M+H, 70).

10

15

Anal. Calcd for: C ₁₁ H ₁₇ N ₅ O ₄ P ₁ Na ₁ · H ₂ O	C, 37.18;	H, 5.38;	N, 19.71.
Found:	C, 37.11;	H, 5.49;	N, 19.71.

EXAMPLE 20

PMEA, cyclic (2,2-dimethyl)propanyl diester

20

Mp 224-226°C. ^1H NMR (d_6 -DMSO) 8.11 (2H, s, H-8, H-2), 7.21 (2H, s, NH₂), 4.34 (2H, t, J=5.0, H-1'), 3.99 (2H,
 d, J=8.7, H-4'), 3.91 (2H, t, J=5.0, H-2'), 3.95-3.75 (4H, m, CH₂C(CH₃)₂CH₂), 1.06 (3H, s, CH₃), 0.67 (3H, s, CH₃).
 ^{13}C NMR (d_6 -DMSO; 50 MHz) 155.89 (C-6), 152.33 (C-2), 149.53 (C-4), 140.86 (C-8), 118.57 (C-5), 76.67
 (CH₂C(CH₃)₂CH₂, d, J=6.8), 70.44 (C-2', d, J=13.7), 64.43 (C-4', d, J=157), 42.43 (C-1'), 31.70 (C(CH₃)₂, d, J=7.6),
 21.05 (CH₃), 19.46 (CH₃). IR (KBr) 3417, 3324, 3152, 2970, 1668, 1650, 1602. MS (FAB) 342 (M+H, 100).

25

30

Anal. Calcd for: C ₁₃ H ₂₀ N ₅ O ₄ P · 0.25 H ₂ O	C, 45.18;	H, 5.97;	N, 20.27.
Found:	C, 45.58;	H, 6.05;	N, 20.05.

EXAMPLE 21

35

PMEA, mono-(3-hydroxypropyl ester) (sodium salt)

^1H NMR (d_6 -DMSO) 8.17 (1H, s, H-8), 8.11 (1H, s, H-2), 7.20 (2H, s, NH₂), 5.11 (1H, t, OH), 4.28 (2H, t, J=4.7, H-1'),
 3.76 (2H, t, J=4.7, H-2'), 3.64 (2H, q, J=6.6, CH₂CH₂OP), 3.41 (2H, d, J=8.0, H-4'), 3.35 (2H, t, J=6.2, HOCH₂),
 1.45 (2H, m, HOCH₂CH₂). ^{13}C NMR (d_6 -DMSO; 50 MHz) 155.82 (C-6), 152.25 (C-2), 149.43 (C-4), 141.38 (C-8),
 118.43 (C-5), 69.77 (C-2', d, J=10), 67.42 (C-4', d, J=152), 59.33 (CH₂CH₂OP, d, J=6), 56.88 (HOCH₂), 42.60 (C-1'),
 33.91 (HOCH₂CH₂; d, J=4). IR (KBr) 3412, 2956, 1647, 1604, 1482, 1421. MS (FAB) 354 (M+H, 17).

45

Anal. Calcd for: C ₁₁ H ₁₇ N ₅ O ₅ P ₁ Na ₁ · 2.5 H ₂ O	C, 33.17;	H, 5.56;	N, 17.59.
Found:	C, 33.32;	H, 5.28;	N, 17.63.

50

EXAMPLE 22

55

PMEA, mono-(octyl ester)

^1H NMR (d_5 -pyridine) 9.47, 9.34 (2H, 2s, H-2, H-8), 5.46 (2H, t, J=4.5), 5.3-5.1 (6H, m, H-2', H-4', CH₂CH₂CH₂O),
 2.68 (2H, m, CH₂CH₂CH₂O), 2.33 (2H, m, CH₂CH₂CH₂O), 2.1 (8H, m, CH₃(CH₂)₄), 1.79 (3H, t, J=6.5, CH₃). IR
 (KBr) 3416, 2928, 1690, 1065. MS (FAB) 386 (M+H, 100).

5

Anal. Calcd for C ₁₆ H ₂₈ N ₅ O ₄ P · H ₂ O · Na · 0.6 NaCl Found:	C, 41.59; C, 41.80;	H, 6.54; H, 6.87;	N, 15.15. N, 15.02.
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EXAMPLE 23

10 PMEA, mono-(3-amino-2,2-dimethylpropyl amide)

¹H NMR (D₂O) 8.13 (1H, s, H-8), 8.11 (1H, s, H-2), 4.36 (2H, t, J=5, H-1'), 3.90 (2H, t, J=5, H-2'), 3.53 (2H, d, J=8.5, H-4'), 2.71 (2H, s, NH₂CH₂) 2.07 (2H, d, J=9.4, CH₂NH), 0.70 (6H, s, CH₃). ¹³C NMR (D₂O) 157.25 (C-6), 154.19 (C-2), 150.78 (C-4), 144.73 (C-8), 120.03 (C-5), 72.24 (C-2', d, J=12.5), 69.63 (C-4', d, J=143), 50.05 (CH₂NH), 48.41 (H₂NCH₂), 45.53 (C-1), 35.36 (C(CH₃)₂, d, J=4), 24.09 (CH₃). IR (KBr) 3786, 3381, 1648, 1605, 1478. MS (FAB) 380 (M+H, 20). HR-MS (M+H)

20

Anal. Calcd for C ₁₃ H ₂₃ N ₇ O ₃ P ₁ Na ₁ : Found:	380.1576. 380.1567.
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25 EXAMPLE 24

PMEA, mono-(hydroxy-2,2-dimethylpropyl ester)

¹H NMR (d₆-DMSO) 8.14 (1H, s, H-8), 8.09 (1H, s, H-2), 7.16 (2H, s, NH₂), 5.84 (1H, t, OH), 4.27 (2H, t, J=4.9, H-1'), 3.77 (2H, t, J=4.9, H-2'), 3.33 (2H, d, J=8.7, H-4'), 3.24 (2H, d, J=10, C(CH₃)₂CH₂OP), 3.00 (2H, d, HOCH₂), 0.63 (6H, s, CH₃). ¹³C NMR (d₆-DMSO, 50 MHz), 155.84 (C-6), 152.21 (C-2), 149.45 (C-4), 141.26 (C-8), 118.48 (C-5), 69.71 (C-2', d, J=9.2), 68.27 (C(CH₃)₂CH₂OP, d, J=6.2), 67.48 (C-4', d, J=152), 65.93 (HOCH₂), 42.57 (C-1'), 36.71 (C(CH₃)₂, d, J=2.5), 21.35 (CH₃). IR (KBr) 3426, 2960, 2883, 1645, 1478, 1417. MS (FAB) 360 (M+H, 100).

35

40

Anal. Calcd. for C ₁₃ H ₂₂ N ₅ O ₅ P · 1.3 H ₂ O: Found:	C, 40.77; C, 40.96;	H, 6.48; H, 6.16;	N, 18.29. N, 17.95
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EXAMPLE 25

PMEA, cyclic (2,2-dimethyl-propenyl diamide)

45

¹H NMR (d₆-DMSO) 8.11 (1H, s, H-8), 8.10 (1H, s, H-2), 7.18 (2H, s, NH₂), 4.30 (2H, t, J=5.0, H-1'), 3.83 (2H, t, J=5.0, H-2'), 3.63 (2H, d, J=7.5, H-4'), 4.27 (2H, s, NH, NH), 2.65-2.40 (4H, m, CH₂C(CH₃)₂CH₂), 0.98 (3H, s, CH₃), 0.64 (3H, s, CH₃). ¹³C NMR (d₆-DMSO) 156.01 (C-6), 152.42 (C-2), 149.60 (C-4), 141.24 (C-8), 118.68 (C-5), 70.35 (C-2', d, J=11.2), 68.53 (C-4', d, J=131), 52.72 (CH₂C(CH₃)₂CH₂, d, J=2.3), 42.78 (C-1'), 30.54 (C(CH₃)₂, d, J=5.6), 24.82 (CH₃), 23.25 (CH₃). IR (KBr) 3100, 2980, 2940, 1650, 1605. MS (FAB) 340 (M+H, 100). HR-MS (M+H)

55

Anal. Calcd for C ₁₃ H ₂₂ N ₇ O ₂ P: Found:	340.1651. 340.1647.
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• EXAMPLE 26

PMEA, N,N'-dimethyl-cyclic propanyl diamide

5 ^1H NMR (d_6 -DMSO) 8.08 (2H, s, H-8, H-2), 7.14 (2H, s, NH₂), 4.28 (2H, br s, H-1'), 3.80 (2H, br s, H-2'), 3.73 (2H, dd, J=7.6, 2.8 Hz), 2.85-2.60 (4H, m, CH₃NCH₂), 1.8-1.3 (2H, m, CH₂CH₂CH₂), 2.36 (3H, d, J=3, NCH₃), 2.33 (3H, d, J=3, NCH₃). ^{13}C NMR (d_6 -DMSO) 156.02 (C-6), 152.44 (C-2), 149.77 (C-4), 141.09 (C-8), 118.74 (C-5), 70.44 (C-2', d, J=14), 65.42 (C-4', d, J=164), 50.22 (NCH₃), 42.85 (C-1), 34.28 (CH₃NCH₂), 24.79 (CH₂CH₂CH₂). IR (KBr) 3300, 3180, 2930, 2877, 1651, 1600. MS (methane/DCI) 340 (M+H, 100).

10

15

Anal. Calcd for C ₁₃ H ₂₂ N ₇ O ₂ P · 0.9 HCl:	C, 41.93;	H, 6.22;	N, 26.33.
Found:	C, 42.33;	H, 6.19;	N, 25.93.

20

HR-MS (M+H) Calcd for C ₁₃ H ₂₂ N ₇ O ₂ P:	340.1651.
Found:	340.1649.

25 EXAMPLE 27

PMEA,mono-(N,N'-diethylacetamide ester)

30 Mp 189-191°C. ^1H NMR (d_6 -DMSO) 8.16 (1H, s, H-8), 8.14 (1H, s, H-2), 7.55 (2H, s, NH₂), 4.80 (2H, d, J=9.0, C(O)CH₂O), 4.31 (2H, t, J=5.0, H-1'), 4.03 (2H, t, J=5.0, H-2'), 3.74 (2H, d, J=8.5, H-4'), 3.22 (2H, q, J=7, CH₃CH₂), 3.16 (2H, q, J=7, CH₃CH₂), 1.01 (3H, t, J=7, CH₃), 1.01 (3H, t, J=7, CH₃). ^{13}C NMR (CF₃CO₂D; 90 MHz) 166.10 (C=O), 150.04, 148.67 (C-6, C-4), 144.74, 144.55 (C-2, C-8), 117.96 (C-5), 70.05 (C-2', d, J=10), 65.37 (C-4', d, J=162), 62.87 (C(O)CH₂, d, J=5), 43.44 (C-1'), 14.06 (CH₃), 12.91 (CH₃). IR (KBr) 3392, 3093, 1692, 1650, 1515. MS (methane/DCI) 500 (M+H, 30), 132 (100). HR-MS (M+H)

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40

Anal. Calcd for C ₁₄ H ₂₃ N ₆ O ₅ P:	387.1546.
Found:	387.1543.

EXAMPLE 28

PMEA, mono-(acetic acid ester)

45 Mp 197-200°C. ^1H NMR (d_6 -DMSO) 8.19 (1H, s, H-8), 8.17 (1H, s, H-2), 7.75 (2H, s, NH₂), 4.34 (2H, d, J=4, C(O)CH₂O), 4.32 (2H, t, J=5, H-1'), 3.86 (2H, t, J=5, H-2'), 3.71 (2H, d, J=8, H-4'). ^{13}C NMR (d_6 -DMSO) 177.19 (C=O, d, J=7), 156.84 (C-6), 153.72 (C-2), 150.03 (C-4), 144.05 (C-8), 119.44 (C-5), 71.66 (C-2', d, J=11), 67.39 (C-4', d, J=157), 64.90 (C(O)CH₂O, d, J=6), 44.59 (C-1'). IR (KBr) 3366, 3109, 1690, 1611, 1516, 1415. MS (FAB) 332 (M+H, 55).

55

Anal. Calcd for C ₁₀ H ₁₄ N ₅ O ₆ P · 0.3 H ₂ O:	C, 35.74;	H, 4.38;	N, 20.85.
Found:	C, 35.41;	H, 4.43;	N, 20.60.

EXAMPLE 29

PMEA di-(butylacetate ester)

5 Mp 78-80°C. ^1H NMR (d_6 -DMSO) 8.11 (1H, s, H-8), 8.06 (1H, s, H-2), 7.18 (2H, s, NH_2), 4.62 (4H, d, J=11, C(O)CH₂OP), 4.31 (2H, t, J=5.0, H-1), 4.07 (4H, t, J=7, CH₂OC(O)), 4.00 (2H, d, J=8, H-4'), 3.90 (2H, t, J=5, H-2'), 1.54 (4H, apparent quintet, J=7, CH₃CH₂CH₂), 1.31 (4H, apparent hexet, J=7, CH₃CH₂). 6.86 (6H, t, J=7, CH₃). ^{13}C NMR (d_6 -DMSO) 168.16 (C=0, d, J=4.7), 156.03 (C-6), 152.44 (C-2), 149.59 (C-4), 141.10 (C-8), 118.65 (C-5), 70.58 (C-2', d, J=10), 64.70 (CH₂OC(O)), 64.19 (C-4', d, J=165), 62.05 (CH₂OP, d, J=6), 42.45 (C-1), 30.10 (CH₃CH₂CH₂), 18.53 (CH₃CH₂), 13.56 (CH₃). IR (KBr) 3339, 3158, 2994, 2962, 1764, 1662, 1600. MS (methane/DCI) 502 (M+H, 100).

15

Anal. Calcd for C ₂₀ H ₃₂ N ₅ O ₈ P:	C, 47.90;	H, 6.43;	N, 13.97.
Found:	C, 47.94;	H, 6.40;	N, 13.90.

EXAMPLE 30

20

PMEA di-(ethylacetate ester)

25 Mp 82-84°C. ^1H NMR (d_6 -DMSO) 8.11 (1H, s, H-8), 8.06 (1H, s, H-2), 7.16 (2H, s, NH_2), 4.59 (4H, d, J=11, C(O)CH₂O), 4.30 (2H, t, J=5.0, H-1), 4.13 (4H, q, J=7.0, CH₃CH₂), 4.00 (2H, d, J=8.0, H-4'), 3.98 (2H, t, J=5.0, H-2'), 1.18 (6H, t, J=7.0, CH₃). ^{13}C NMR (D₂O) 171.44 (C=O, d, J=5), 156.90 (C-6), 153.85 (C-2), 150.56 (C-4), 144.66 (C-8), 119.86 (C-5), 73.02 (C-2', d, J=10.5), 66.12 (C-4', d, J=166), 64.85 (CH₃CH₂), 64.75 (C(O)CH₂O), 45.57 (C-1) 15.22 (CH₃). IR (KBr) 3296, 3122, 1764, 1667, 1602. MS (methane/DCI) 446 (M+H, 100).

30

Anal. Calcd for C ₁₆ H ₂₄ N ₅ O ₈ P:	C, 43.15;	H, 5.43;	N, 15.72.
Found:	C, 43.04;	H, 5.33;	N, 15.58.

35

EXAMPLE 31

PMEA mono-(phenyl ester) (sodium salt)

40 Mp 223-228°C. ^1H NMR (d_6 -DMSO) 8.14 (1H, s, H-8), 8.13 (1H, s, H-2), 7.50 (2H, s, NH_2), 7.25 (2H, t, J=8, ArH), 7.07 (1H, t, J=8, ArH), 7.01 (2H, d, J=8, ArH), 4.33 (2H, t, J=5, H-1), 3.89 (2H, t, J=5, H-2'), 3.73 (2H, d, J=8, H-4'), ^{13}C NMR (D₂O; Partial spectrum) 131.46, 126.06 (ArC), 122.27 (ArC, d, J=3.5), 72.27 (C-2; d, J=12), 67.68 (C-4', d, J=160), 46.08 (C-1). IR (KBr) 3389, 3068, 1693, 1594. MS (FAB) 350 (M+H, 40).

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Anal. Calcd for C ₁₄ H ₁₆ N ₅ O ₄ P · H ₂ O · 0.45 Na:	C, 44.45;	H, 4.81;	N, 18.51.
Found:	C, 44.45;	H, 4.45;	N, 18.45.

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EXAMPLE 32

PMEA di-(phenyl ester)

55 Mp 103-114°C. ^1H NMR (d_6 -DMSO) 8.15 (1H, s, H-8), 8.11 (1H, s, H-2), 7.40 (2H, s, NH_2), 7.34 (4H, t, J=7, ArH), 7.20 (2H, t, J=7, ArH), 7.04 (4H, t, J=7, ArH), 4.38 (2H, t, J=5, H-1), 4.24 (2H, d, J=8, H-4'), 3.98 (2H, t, J=5, H-2'), ^{13}C NMR (d_6 -DMSO) 155.51 (C-6), 151.77 (C-2), 149.57 (C-4), 141.46 (C-8), 130.02, 125.49, (ArC), 120.56 (ArC, d, J=4), 118.71 (C-5), 70.58 (C-2', d, J=12), 63.52 (C-4', d, J=164), 42.68 (C-1'). IR (KBr) 3270, 3100, 1675, 1646,

1601, 1490. MS (FAB) 426 (M+H, 100).

5

Anal. Calcd for C ₂₀ H ₂₀ N ₅ O ₄ P · 0.25 H ₂ O:	C, 55.87;	H, 4.81;	N, 16.29.
Found:	C, 55.80;	H, 4.65;	N, 15.98.

EXAMPLE 33

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PMEA, mono-(N,N-diisopropylacetamide ester) (sodium salt)

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Mp 219-221°C. ¹H NMR (d₆-DMSO) 8.14 (1H, s, H-8), 8.13 (1H, s, H-2), 7.37 (2H, s, NH₂), 4.45 (2H, d, J=9, CH₂OP), 4.31 (2H, t, J=5, H-1'), 3.88 (2H, t, J=5, H-2'), 3.74 (2H, d, J=8, H-4'), 3.43 (2H, m, CH(CH₃)₂), 1.26 (6H, d, J=6, CH₃), 1.08 (6H, d, J=6, CH₃). ¹³C NMR (d₆-DMSO/D₂O) 170 (C=O), 156.90 (C-6), 153.89 (C-2), 150.35 (C-4), 144.29 (C-8), 119.68 (C-5), 71.89 (C-2', d, J=12), 67.81 (C-4', d, J=158), 65.25 (CH₂OP, d, J=5), 49.72 (CH(CH₃)₂), 47.30 (CH(CH₃)₂), 45.00 (C-1), 21.21 (CH₃). IR (KBr) 3425, 2969, 1691, 1643, 1515. MS (FAB) 415 (M+H, 100).

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Anal. Calcd for C ₁₆ H ₂₇ N ₆ O ₅ P · 0.67 H ₂ O · 0.5 Na:	C, 43.87;	H, 6.52;	N, 19.19.
Found:	C, 43.92;	H, 6.17;	N, 18.79.

25

EXAMPLE 34

PMEA, di-(p-nitrobenzyl ester)

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Mp 190-193°C. ¹H NMR (d₆-DMSO) 8.16 (4H, d, J=8, ArH), 8.09 (1H, s, H-8), 8.08 (1H, s, H-2), 7.51 (4H, d, J=8, ArH), 7.17 (2H, s, NH₂), 5.10 (4H, d, J=8, ArCH₂O), 4.32 (2H, t, J=5, H-1'), 4.07 (2H, d, J=8, H-4'), 3.90 (2H, t, J=5, H-2'). ¹³C NMR (d₆-DMSO) 155.97 (C-6), 152.94 (C-2), 149.62 (C-4), 147.19, 143.96 (ArC), 141.13 (C-8), 128.15, 123.56 (ArC), 118.65 (C-5), 70.62 (C-2', d, J=7), 65.86 (ArCH₂O, d, J=6), 63.75 (C-4', d, J=162), 42.49 (C-1). IR (KBr) 3420, 3268, 3110, 1674, 1642, 1604. MS (FAB) 544 (M+H, 60).

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Anal. Calcd for C ₂₂ H ₂₂ N ₇ O ₈ P:	C, 48.63;	H, 4.09;	N, 18.05.
Found:	C, 48.61;	H, 4.01;	N, 18.04.

EXAMPLE 35

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PMEA, mono-(p-nitrobenzyl ester) (sodium salt)

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Mp 230-240°C. ¹H NMR (d₆-DMSO) 8.19 (2H, d, J=8.6, ArH), 8.12 (1H, s, H-8), 8.11 (1H, s, H-2), 7.54 (2H, d, J=8.6, ArH), 4.93 (2H, d, J=7.7, ArCH₂O), 4.63 (2H, t, J=5, H-1'), 4.31 (2H, t, J=5, H-2'), 3.72 (2H, d, J=8.6, H-4'). IR (KBr) 3742, 1930, 1692, 1606, 1518. MS (FAB) 409 (M+H, 27).

55

Anal. Calcd for C ₁₅ H ₁₇ N ₆ O ₆ P · 0.75 H ₂ O · 0.5 Na:	C, 41.58;	H, 4.30;	N, 19.40.
Found:	C, 41.37;	H, 3.92;	N, 19.03.

EXAMPLE 36

PMEA, di-(2,2,2-trichloroethyl ester)

5 Mp 155-157°C. ^1H NMR (d_6 -DMSO) 8.11 (1H, s, H-8), 8.08 (1H, s, H-2), 7.16 (2H, s, NH₂), 4.68 (2H, d, J=7, CCl₃CH₂), 4.67 (2H, d, J=7, CCl₃CH₂), 4.34 (2H, t, J=5, H-1), 4.18 (2H, d, J=8, H-4'), 3.95 (2H, t, J=5, H-2'). ^{13}C NMR (d_6 -DMSO) 156.09 (C-6), 152.59 (C-2), 149.71 (C-4), 141.28 (C-8), 118.75 (C-5), 95.42 (CCl₃, d, J=8.6), 75.48 (CCl₃CH₂, d, J=5.7), 70.92 (C-2' d, J=7), 63.99 (C-4', d, J=163), 42.72 (C-1'). IR (KBr) 3372, 3334, 3210, 1658, 1604, 1576. MS (methane/DCI) 536 (100), 534 (50), 192 (95).

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Anal. Calcd for C ₁₂ H ₁₄ N ₅ O ₁₄ PCl ₆ :	C, 26.89;	H, 2.63;	N, 13.07.
Found:	C, 26.85;	H, 2.55;	N, 12.86.

EXAMPLE 37

PMEA, mono-(2,2,2-trichloroethyl ester)

20 Mp 218-225°C. ^1H NMR (d_6 -DMSO) 8.51 (2H, s, NH₂), 8.30, 8.24 (2H, 2s, H-8, H-2), 4.36 (2H, t, J=5, H-1'), 4.33 (2H, d, J=6, Cl₃CCH₂), 3.72 (2H, d, J=8, C-4'), 3.91 (2H, t, J=5, H-2'). ^{13}C NMR (d_6 -DMSO) 153.03 (C-6), 148.91 (C-2), 148.22 (C-4), 142.78 (C-8), 118.27 (C-5), 97.05 (CCl₃), 75.67 (CCl₃CH₂, d, J=5), 69.99 (C-2', d, J=10), 66.17 (C-4', d, J=159), 43.12 (C-1'). IR (KBr) 3424, 1930, 1690, 1614, 1514, 1414. MS (methane/DCI) 404 (M+H, 1), 136 (40), 113 (100).

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Anal. Calcd for C ₁₀ H ₁₃ N ₅ O ₄ PCl ₃ • 0.3 CCl ₃ CH ₂ OH:	C, 28.34;	H, 3.05;	N, 15.59.
Found:	C, 28.19;	H, 3.17;	N, 15.59.

EXAMPLE 38

PMEA, di-(benzoyloxyethyl ester)

35 Mp 49-52°C. ^1H NMR (d_6 -DMSO) 8.09 (1H, s, H-8), 7.99 (1H, s, H-2), 7.92 (4H, d, J=7, ArH), 7.67 (2H, t, J=7.5, ArH), 7.49 (2H, t, J=7.5, ArH), 7.18 (2H, s, NH₂), 5.82 (4H, d, J=13, OCH₂O), 4.22 (2H, t, J=5, H-1'), 4.04 (2H, d, J=8, H-4'), 3.82 (2H, d, J=5, H-2'). ^{13}C NMR (d_6 -DMSO) 164.35 (C=0), 156.02 (C-6), 152.45 (C-2), 149.55 (C-4), 140.99 (C-8), 134.22 (ArH), 129.60 (ArH), 128.98 (ArH), 128.35 (ArH), 118.70 (C-5), 70.62 (C-2', d, J=11.5), 64.17 (C-4', d, J=163), 42.29 (C-1'). IR (KBr) 3328, 3182, 1739, 1644, 1602. MS (FAB) 542 (M+H, 45).

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45

Anal. Calcd for C ₂₄ H ₂₄ N ₅ O ₆ P • 0.66 H ₂ O:	C, 52.09;	H, 4.61;	N, 12.65.
Found:	C, 52.09;	H, 4.36;	N, 12.37.

EXAMPLE 39

PMEA, di-(p-trifluoromethyl benzyl ester)

50 Mp 115-125°C. ^1H NMR (d_6 -DMSO) 8.18 (1H, s, H-8), 8.17 (1H, s, H-2), 7.66 (4H, d, J=8, ArH), 7.47 (4H, d, J=8, ArH), 7.57 (2H, s, NH₂), 5.09 (4H, d, J=8, ArCH₂), 4.35 (2H, t, J=5, H-1'), 4.04 (2H, d, J=8, H-4'), 3.91 (2H, t, J=5, H-2'). ^{13}C NMR (d_6 -DMSO) 154.99 (C-6), 151.13 (C-2), 149.44 (C-4), 141.7 (C-8), 141.12 (ArC), 128.63 (CF₃-ArC, q, J=31.8), 127.93, 125.31 (ArC), 124.17 (CF₃, q, J=275), 118.53 (C-5), 70.46 (C-2', d, J=11), 66.14 (ArCH₂, d, J=5.5), 63.78 (C-4', d, J=161), 42.61 (C-1'). IR (KBr) 3292, 3118, 1670, 1602, 1476. MS (FAB) 590 (M+H, 100).

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Anal. Calcd for C ₂₄ H ₂₂ N ₅ O ₄ PF ₆ · 0.5 H ₂ O:	C, 48.17;	H, 3.87;	N, 11.70.
Found:	C, 47.81;	H, 3.55;	N, 11.30.

EXAMPLE 40**10 PMEA mono-(2,2-difluoro-3-hydroxypropyl ester)**

¹H NMR (d₆-DMSO) 8.20 (2H, s, H-8, H-2), 7.80 (2H, s, NH₂), 4.34 (2H, t, J=5.0, H-1'), 4.04 (2H, dt, J=13.2, 7.9), CF₂CH₂OP), 3.87 (2H, t, J=5.0, H-2'), 3.70 (2H, d, J=8.0, H-4'). 3.60 (2H, t, J=13, HOCH₂). ¹³C NMR (D₂O/NaOD) 157.34 (C-6), 154.24 (C-2), 150.67 (C-4), 144.72 (C-8), 123.54 (CF₂, t, J=30), 120.12 (C-5), 72.40 (C-2', d, J=12), 67.75 (C-4', d, J=159), 64.94 (CF₂CH₂OP, dt, J=30, 5), 63.28 (HOCH₂, d, J=27), 45.49 (C-1'). IR (KBr) 3310, 3112, 1694, 1602, 1514. MS (FAB) 368 (M+H, 55). HR-MS (M+H).

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Anal. Calcd for C ₁₁ H ₁₆ N ₅ O ₅ F ₂ P:	368.0935.
Found:	368.0930.

EXAMPLE 41**25 PMEA mono-(p-trifluoromethylbenzyl ester)**

¹H NMR (d₆-DMSO) 8.13 (2H, s, H-8, H-2), 7.69 (2H, d, J=8, ArH), 7.49 (2H, d, J=8, ArH), 7.34 (2H, s, NH₂), 4.92 (2H, d, J=8, ArCH₂O), 4.32 (2H, t, J=5, C-1'), 3.87 (2H, t, J=5, H-2'), 3.75 (2H, d, J=8, H-4'). IR (KBr) 3062, 1696, 1602, 1514, 1418. MS (FAB) 432 (M+H, 80). HR-MS (M+H).

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Anal. Calcd for C ₁₆ H ₁₇ N ₅ O ₄ PF ₃ :	432.1048.
Found:	432.1039.

EXAMPLE 42**40 PMEA dibutylamide**

Mp 117-119°C. ¹H NMR (d₆-DMSO) 8.12 (2H, s, H-8, H-2), 7.19 (2H, s, NH₂), 4.29 (2H, t, J=5, H-1'), 3.82 (2H, t, J=5, H-2'), 3.83 (2H, s, NH), 3.52 (2H, d, J=8, H-4'), 2.64 (4H, m, CH₂NH), 1.24 (8H, m, CH₃CH₂CH₂), 0.80 (6H, t, J=7, CH₃). ¹³C NMR (d₆-DMSO) 155.98 (C-6), 152.61 (C-2), 149.71 (C-4), 141.52 (C-8), 118.65 (C-5), 70.46 (C-2', d, J=11), 67.28 (C-4', d, J=131), 42.83 (C-1'), 39.22 (NHCH₂), 34.10 (NHCH₂CH₂), 19.59 (CH₃CH₂), 13.92 (CH₃). IR 3278, 3242, 2952, 2928, 2872, 1682, 1608. MS (FAB) 384 (M+H, 100).

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Anal. Calcd for C ₁₆ H ₃₀ N ₇ O ₂ P:	C, 50.12;	H, 7.89;	N, 25.57.
Found:	C, 49.77;	H, 7.79;	N, 25.30.

EXAMPLE 43**55 PMEA di-(2-methylpropyl ester)**

Mp 109-110°C. ¹H NMR(d₆-DMSO) 8.10(1H, S, H-8) 8.05(1H, S, H-2), 7.19(2H, S, NH₂), 4.31(2H, t, J=5.0, H-1'),

3.87(2H,t,J=5.0,H-2'), 3.85 (2H,d,J=8.5,H-4), 3.61(4H,dt,J=6.8,1.4,CH₂OP), 1.72(2H, apparent heptet, J=6.7,CH), 0.77(12H,d,J=6.7,CH₃). ¹³C NMR (d₆-DMSO) 156.04(C-6), 152.42(C-2), 149.60(C-4), 141.05(C-8), 118.69(C-5), 71.42(CH₂OP, d, J=6.7), 70.36(C-2',d,J=11.6), 63.65(C-4',d,J=163), 42.52(C-1'), 28.72(CH,d,J=5.7), 18.45(CH₃). IR(KBr) 3286, 3104, 2960, 1670, 1600. MS(FAB) 386(M+H, 100).

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Anal. Calcd for C ₁₆ H ₂₈ N ₅ O ₄ P ₁ :	C, 49.86;	H, 7.32;	N, 18.17.
Found:	C, 49.81;	H, 7.26;	N, 18.11

EXAMPLE 44

PMEA, di-(3-methylbutyl ester)

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Mp 94-98°C. ¹H NMR(CDCl₃) 8.30(1H, S, H-8) 7.94(1H, S, H-2), 6.21(2H, S, NH₂), 4.37(2H, t, J=5.0, H-1), 4.01(4H,dt, J=6.8, 6.8, CH₂OP), 3.91(2H, t, J=5.0, H-2'), 3.75(2H,d,J=8.0,H-4), 1.63 (2H, apparent heptet, J=6.6, CH), 1.47(4H,dt, J=6.7, 6.7, CH₂CH₂OP), 0.84(12H,d,J=6.5,CH₃). ¹³C NMR (CDCl₃) 155.28(C-6), 152.38(C-2), 150.38(C-4), 141.70(C-8), 119.76(C-5), 71.13(C-2',d,J=10.0), 65.17(C-4',d,J=166), 65.02 (CH₂OP,d,J=6.8), 43.46(C-1'), 39.19 (CH₂CH₂OP,d,J=5.7), 24.50(CH), 22.31(CH₃), 22.29(CH₃). IR(KBr) 3282, 3106, 2958, 1672, 1600, 1478. MS(methane/DCl) 414(M+H,100).

25

Anal. Calcd. for C ₁₈ H ₃₂ N ₅ O ₄ P ₁ · 0.75H ₂ O:	C, 50.63;	H, 7.91;	N, 16.40.
Found:	C, 50.67;	H, 7.66;	N, 16.26.

Claims

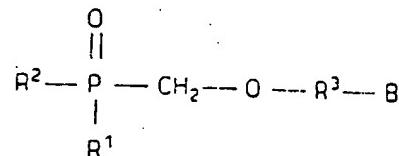
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Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound having the structural formula I

35

40



FORMULA I

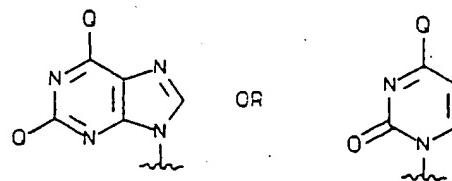
45

wherein

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B represents adenine (A), cytosine (C), guanine (G), thymine (T), uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx).

55



10 wherein

Q is independently chosen from H, Cl, NHR⁵, NR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH or NCHN(R⁵)₂; R¹ and R² are identical or different and independently of one another are each OR⁴, NH₂, NHR⁵ or N(R⁵)₂; R¹ and R² optionally being linked with each other to form a cyclic group, or R¹ or R² optionally being linked to R³ to form a cyclic group;

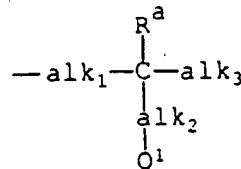
15 R³ represents C₁-C₂₀ alkylene which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen; or R³ is CH(CH₂OR⁶)CH₂, whereby R¹ and R² each independently may additionally represent OH, and R⁶ is a hydrolyzable ester group;

20 R⁴ represents a physiologically hydrolyzable ester group selected from CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R; S; or RS stereochemistry), CH₂C(R⁵)₂CH₂OH, or CH₂OR⁵; or R⁴ represents C₄-C₂₀ alkyl, aryl-alkyl or aryl which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen provided that R¹ and R² are not simultaneously alkoxy;

25 R⁵ represents C₁-C₂₀ alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy and halogen; pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof; provided that those compounds of the above formula I are excluded wherein

B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil, R³ is

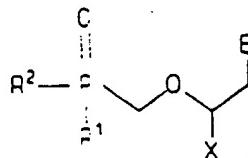
30



wherein alk₁ is bonded to B, alk₁, alk₂ and alk₃ are independently selected from a chemical bond or C₁-C₄ alkylene, R^a is hydrogen or C₁-C₄ alkyl and Q¹ is hydrogen or hydroxyl, and R¹ and R² are unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy.

40 2. The compound of claim 1 which has the general structural formula II

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FORMULA II

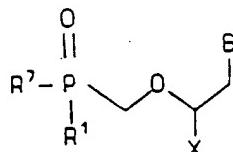
55 wherein

B, R¹ and R² are as described in claim 1, provided that when Q is NCHN(R⁵)₂, then R⁵ is not CH₃; X represents hydrogen, CH₂OR⁶ (R; S; or RS stereochemistry), or substituted or unsubstituted lower alkyl, in

particular methyl or hydroxymethyl; when X is CH_2OR^6 , R^1 and R^2 may additionally be independently chosen from OH; and
 R^6 is a hydrolyzable ester group.

5. 3. A compound having the general structural formula III

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15

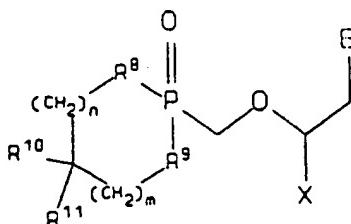
FORMULA III

wherein

20 B , and R^1 are as previously described in claim 1;
 X represents hydrogen, CH_2OR^6 (R^6 ; or R^6 stereochemistry) or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH_2OR^6 , R^1 may additionally be OH; and R^6 is a hydrolyzable ester group;
25 R^7 represents OH, NH_2 , NHR^5 , or NR^5_2 ; and
 R^5 is as described in claim 1; pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof;
provided that those compounds of the above formula III are excluded wherein
30 B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil,
 X is alk₂-Q¹ wherein alk₂ is selected from a chemical bond or C₁-C₄ alkylene, Q¹ is hydrogen or hydroxyl, and
 R^1 and R^7 are OH, unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy.

4. The compound of claim 1 which has the general structural formula IV

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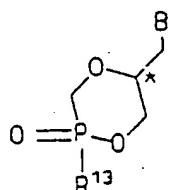
45

FORMULA IV

wherein

50 R^8 and R^9 are identical or different and independently of one another are each NR^{12} , or oxygen;
 R^{10} and R^{11} are identical or different and independently of one another are each hydrogen, or R^5 ;
 R^{12} represents hydrogen or a lower alkyl;
 m and n are identical or different and independently of one another are each 0 or 1;
55 B and R^5 are as described in claim 1; and
 X is as described in claim 2.

5. The compound which has the general structural formula V



* stereochemistry is R; S; or RS

FORMULA V

5

10

wherein

R¹³ represents OR⁴, NHR⁵, NR⁵₂, or OH, provided that R¹³ is not OH when B is A or C; and
15 B, R⁴, and R⁵ are as described in claim 1;
pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

20 6. The compound of claim 1, wherein R⁴ is C₄-C₂₀ alkyl, aryl or aryl-alkyl which may be unsubstituted or substituted by substituents independently selected from hydroxy and halogen.

7. The compound of claim 1 wherein R¹ and R² are OR⁴, and R⁴ represents a physiologically hydrolyzable ester group selected from CH₂OC(O)R⁵; and CH(R⁵)OC(O)R⁵ (R,S; or R,S stereochemistry); or aryl wherein aryl is substituted by substituents independently selected from hydroxy and halogen.

25 8. The compound of claim 1 which is

PMEA, di-(propionyloxymethyl ester);
PMEA, di-(isobutyryloxymethyl ester);
PMEA, bis-diethylamide;
30 PMEA, di-(butylacetate ester);
PMEA, di-(ethylacetate ester);
PMEA, di-(benzoyloxyxymethyl ester);
PMEA, dibutylamide;
35 PMEA, di-(2-methylpropyl ester); or
PMEA, di-(3-methylbutyl ester).

9. The compound of claim 1 which is

PMEA, di-(pivaloyloxymethyl ester).
40

10. The compound of claim 3 which is

PMEA, mono-(pivaloyloxymethyl ester);
PMEA, mono-(octyl ester);
45 PMEA, mono-(hydroxy-2,2-dimethylpropyl ester);
PMEA, mono-(2,2,2-trichloroethyl ester); or
PMEA, mono-(2,2-difluoro-3-hydroxypropyl ester).

50 11. The compound of claim 4 which is

PMEA, cyclic propanyl diester;
PMEA, cyclic (2,2-dimethyl)propanyl diester;
PMEA, cyclic (2,2-dimethyl)propanyl diamide;
PMEA, N,N'-dimethyl-cyclic propanyl diamide.
55

12. The compound which is

PMEA, di-(isopropyl ester);

PMEHx, mono-(isopropyl ester);
 6-chloro-9-(2-phosphorylmethoxy)ethylpurine,
 di-(isopropyl ester);
 9-(2-phosphorylmethoxy)ethylpurine, di-(isopropyl ester);
 5 PMEA, mono-(isopropyl ester);
 PMEA, (mono-isopropyl, mono-pivaloyloxymethyl) ester; or
 PMEA, (mono-isopropyl, mono-phenyl) ester;
 pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

10 13. The compound which is

PMEA, di-(phenyl ester);
 PMEA, di-(p-nitrobenzyl ester);
 PMEA, di-(2,2,2-trichloroethyl ester);
 15 PMEA, di-(p-trifluoromethylbenzyl ester);
 PMEA, mono-(choline ester);
 PMEA, (mono-N,N-diethylacetamide, mono-pivaloyloxymethyl) ester;
 PMEA, mono-(3-hydroxypropyl ester);
 PMEA, mono-(3-amino-2,2-dimethylpropyl amide);
 20 PMEA, mono-(N,N-diethylacetamide ester);
 PMEA, mono-(acetic acid ester);
 PMEA, mono-(N,N-disopropylacetamide ester);
 PMEA, mono-(p-nitrobenzyl ester); or
 PMEA, mono-(p-trifluoromethylbenzyl ester);
 25 PMEA, mono-(phenyl ester);
 pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

14. A process for producing the compound of claim 1, 2, 12, or 13 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the 30 appropriate alkyl halide; or hydrolysis of the diethers or diamines.

15. A process for producing the compound of claim 3, 12, or 13 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or hydrolysis of the diethers or diamines.

35 16. A process for producing the compound of claim 4 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol.

17. A process for producing the compound of claim 5 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate 40 alkyl halide.

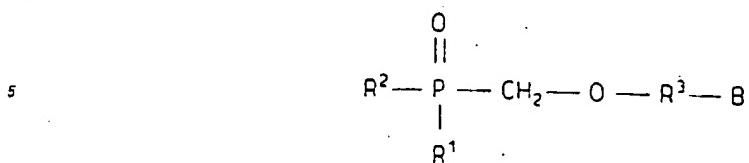
18. The use of a compound as defined in anyone of claims 1 to 13 for preparing a pharmaceutical composition for the treatment of viral infection in a mammal.

45 19. The use of a compound as defined in anyone of claims 1 to 13 for preparing a pharmaceutical composition for inhibiting growth of a tumor in a mammal.

20. A pharmaceutical composition which comprises at least one compound of claims 1 to 13 in association with a pharmaceutically acceptable substantially nontoxic carrier or excipient.

50 Claims for the following Contracting State : ES

1. A process for producing a compound having the structural formula I

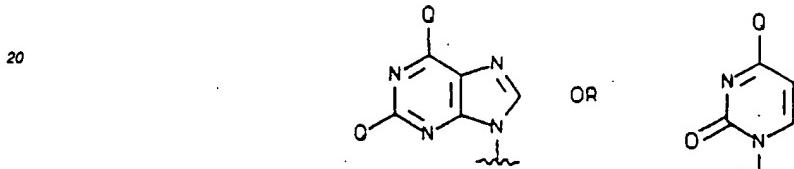


10

FORMULA I

wherein

15 B represents adenine (A), cytosine (C), guanine (G), thymine (T), uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx).



wherein

Q is independently chosen from H, Cl, NHR⁵, NR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH or NCHN(R⁵)₂;

30 R¹ and R² are identical or different and independently of one another are each OR⁴, NH₂, NHR⁵ or N(R⁵)₂; R¹ and R² optionally being linked with each other to form a cyclic group, or R¹ or R² optionally being linked to R³ to form a cyclic group;

R³ represents C₁-C₂₀ alkylene which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen; or R³ is CH(CH₂OR⁶)CH₂, whereby R¹ and R² each independently may additionally represent OH, and R⁶ is a hydrolyzable ester group;

35 R⁴ represents a physiologically hydrolyzable ester group selected from CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R; S; or RS stereochemistry), CH₂C(R⁵)₂CH₂OH, or CH₂OR⁵; or R⁴ represents C₄-C₂₀ alkyl, aryl-alkyl or aryl which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen provided that R¹ and R² are not simultaneously alkoxy;

40 R⁵ represents C₁-C₂₀ alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents independently selected from the group consisting of hydroxy and halogen; pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof;

provided that those compounds of the above formula I are excluded wherein

45 B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil, R³ is

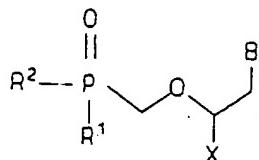


55

wherein alk₁ is bonded to B, alk₁, alk₂ and alk₃ are independently selected from a chemical bond or C₁-C₄ alkylene, R^a is hydrogen or C₁-C₄ alkyl and Q¹ is hydrogen or hydroxyl, and R¹ and R² are unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy;

which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.

- 5 2. The process of claim 1 for producing a compound of claim 1 which has the general structural formula II

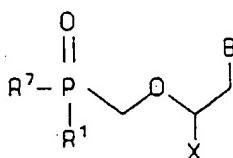


15 FORMULA II

wherein

20 B, R¹ and R² are as described in claim 1, provided that when Q is NCHN(R⁵)₂, then R⁵ is not CH₃; X represents hydrogen, CH₂OR⁶ (R;S; or RS stereochemistry), or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH₂OR⁶, R¹ and R², may additionally be independently chosen from OH; and R⁶ is a hydrolyzable ester group.

- 25 3. A process for producing a compound having the general structural formula III



35 FORMULA III

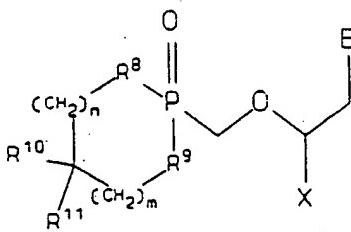
wherein

40 B, and R¹ are as previously described in claim 1; X represents hydrogen, CH₂OR⁶ (R;S; or RS stereochemistry) or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH₂OR⁶, R¹ may additionally be OH; and R⁶ is a hydrolyzable ester group;

45 R⁷ represents OH, NH₂, NHR⁵, or NR⁵₂; and R⁵ is as described in claim 1; pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof; provided that those compounds of the above formula III are excluded wherein

B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil, X is alk₂-Q¹ wherein alk₂ is selected from a chemical bond or C₁-C₄ alkylene, Q¹ is hydrogen or hydroxyl, and R¹ and R⁷ are OH, unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy; which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or hydrolysis of the diethers or diamines.

- 55 4. A process for producing a compound of claim 1 having the general structural formula IV

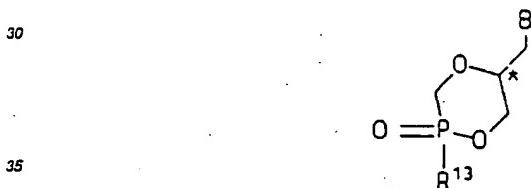


FORMULA IV

15 wherein

20 R^8 and R^9 are identical or different and independently of one another are each NR^{12} , or oxygen;
 R^{10} and R^{11} are identical or different and independently of one another are each hydrogen, or R^5 ;
 R^{12} represents hydrogen or a lower alkyl;
 m and n are identical or different and independently of one another are each 0 or 1;
 B and R^5 are as described in claim 1; and
 X is as described in claim 2;
 25 which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol.

5. A process for producing a compound having the general structural formula V



* stereochemistry is R, S, or RS

40

FORMULA V

45 wherein

50 R^{13} represents OR^4 , NHR^5 , NR^5_2 , or OH , provided that R^{13} is not OH when B is A or C; and
 B , R^4 , and R^5 are as described in claim 1; pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof;
 55 which process comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide.

6. The process of claim 1 for producing a compound of claim 1, wherein R^4 is C_4-C_{20} alkyl, aryl or aryl-alkyl which may be unsubstituted or substituted by substituents independently selected from hydroxy and halogen.
7. The process of claim 1 for producing a compound of claim 1 wherein R^1 and R^2 are OR^4 , and R^4 represents a physiologically hydrolyzable ester group selected from $CH_2OC(O)R^5$; and $CH(R^5)OC(O)R^5$ (R,S, or R S stereochemistry).

• try); or aryl wherein aryl is substituted by substituents independently selected from hydroxy and halogen.

8. The process of claim 1 for producing a compound of claim 1 which is

- 5 PMEA, di-(propionyloxymethyl ester);
PMEA, di-(isobutyryloxymethyl ester);
PMEA, bis-diethylamide;
PMEA, di-(butylacetate ester);
PMEA, di-(ethylacetate ester);
10 PMEA, di-(benzoyloxymethyl ester);
PMEA, dibutylamide;
PMEA, di-(2-methylpropyl ester); or
PMEA, di-(3-methylbutyl ester).

15 9. The process of claim 1 for producing a compound of claim 1 which is

PMEA, di-(pivaloyloxymethyl ester).

10. The process of claim 3 for producing a compound of claim 3 which is

- 20 PMEA, mono-(pivaloyloxymethyl ester);
PMEA, mono-(octyl ester);
PMEA, mono-(hydroxy-2,2-dimethylpropyl ester);
PMEA, mono-(2,2,2-trichloroethyl ester); or
25 PMEA, mono-(2,2-difluoro-3-hydroxypropyl ester).

11. The process of claim 4 for producing a compound of claim 4 which is

- 30 PMEA, cyclic propanyl diester;
PMEA, cyclic (2,2-dimethyl)propanyl diester;
PMEA, cyclic (2,2-dimethyl)propanyl diamide;
PMEA, N,N'-dimethyl-cyclic propanyl diamide.

12. The process of claim 1 or claim 3 for producing a compound which is

- 35 PMEA, di-(isopropyl ester);
PMEHx, mono-(isopropyl ester);
6-chloro-9-(2-phosphonylmethoxy)ethylpurine,
di-(isopropyl ester);
40 9-(2-phosphonylmethoxy)ethylpurine, di-(isopropyl ester);
PMEA, mono-(isopropyl ester);
PMEA, (mono-isopropyl, mono-pivaloyloxymethyl) ester; or
PMEA, (mono-isopropyl, mono-phenyl) ester;
pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

45 13. The process of claim 1 or claim 3 for producing a compound which is

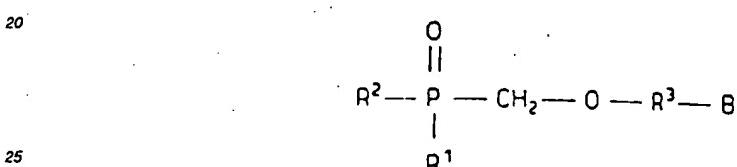
- 50 PMEA, di-(phenyl ester);
PMEA, di-(p-nitrobenzyl ester);
PMEA, di-(2,2,2-trichloroethyl ester);
PMEA, di-(p-trifluoromethylbenzyl ester);
PMEA, mono-(choline ester);
PMEA, (mono-N,N-diethylacetamide, mono-pivaloyloxymethyl) ester;
55 PMEA, mono-(3-hydroxypropanyl ester);
PMEA, mono-(3-amino-2,2-dimethylpropyl amide);
PMEA, mono-(N,N-diethylacetamide ester);
PMEA, mono-(acetic acid ester);
PMEA, mono-(N,N-diisopropylacetamide ester);

PMEA, mono-(p-nitrobenzyl ester); or
 PMEA, mono-(p-trifluoromethylbenzyl ester);
 PMEA, mono-(phenyl ester);
 pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

- 5 14. The use of a compound as defined in anyone of claims 1 to 13 for preparing a pharmaceutical composition for the treatment of viral infection in a mammal.
- 10 15. The use of a compound as defined in anyone of claims 1 to 13 for preparing a pharmaceutical composition for inhibiting growth of a tumor in a mammal.
- 15 16. A process for preparing a pharmaceutical composition which comprises mixing an amount of at least one compound as defined in anyone of claims 1 to 13 with a pharmaceutically acceptable substantially nontoxic carrier or excipient.

15 Claims for the following Contracting State : GR

- 20 1. A compound having the structural formula I

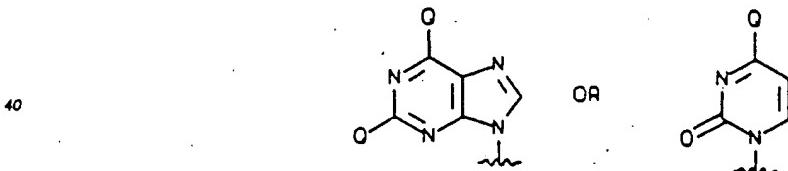


FORMULA I

30 wherein

B represents adenine (A), cytosine (C), guanine (G), thymine (T), uracil (U), 2,6-diamino purine (DAP), hypoxanthine (Hx).

35



45 wherein

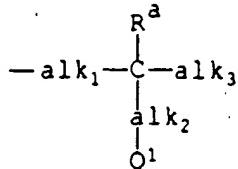
Q is independently chosen from H, Cl, NHR⁵, HR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH or NCHN(R⁵)₂; R¹ and R² are identical or different and independently of one another are each OR⁴, NH₂, NHR⁵ or N(R⁵)₂; R¹ and R² optionally being linked with each other to form a cyclic group, or R¹ or R² optionally being linked to R³ to form a cyclic group;

50 R³ represents C₁-C₂₀ alkylene which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen; or R³ is CH(CH₂OR⁶)CH₂, whereby R¹ and R² each independently may additionally represent OH, and R⁶ is a hydrolyzable ester group;

55 R⁴ represents a physiologically hydrolyzable ester group selected from CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R; S; or RS stereochemistry), CH₂C(R⁵)₂CH₂OH, or CH₂OR⁵; or R⁴ represents C₄-C₂₀ alkyl, aryl-alkyl or aryl which may be unsubstituted or substituted by substituents independently selected from the group consisting of hydroxy and halogen provided that R¹ and R² are not simultaneously alkoxy;

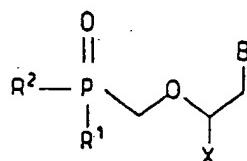
R⁵ represents C₁-C₂₀ alkyl, aryl or aryl-alkyl which may be substituted or unsubstituted by substituents inde-

pendently selected from the group consisting of hydroxy and halogen; pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof;
 provided that those compounds of the above formula I are excluded wherein
 5 B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil,
 R³ is



15 wherein alk₁ is bonded to B, alk₁, alk₂ and alk₃ are independently selected from a chemical bond or C₁-C₄ alkylene, R^a is hydrogen or C₁-C₄ alkyl and Q¹ is hydrogen or hydroxyl, and R¹ and R² are unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy.

20 2. The compound of claim 1 which has the general structural formula II

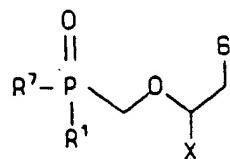


FORMULA II

30 wherein

B, R¹ and R² are as described in claim 1, provided that when Q is NCH(R⁵)₂, then R⁵ is not CH₃;
 35 X represents hydrogen, CH₂OR⁶ (R:S; or RS stereochemistry), or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH₂OR⁶, R¹ and R², may additionally be independently chosen from OH; and
 R⁶ is a hydrolyzable ester group.

40 3. A compound having the general structural formula III



FORMULA III

50 wherein

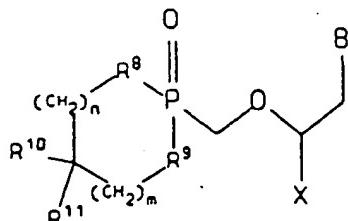
B, and R¹ are as previously described in claim 1;
 55 X represents hydrogen, CH₂OR⁶ (R:S; or RS stereochemistry) or substituted or unsubstituted lower alkyl, in particular methyl or hydroxymethyl; when X is CH₂OR⁶, R¹ may additionally be OH; and R⁶ is a hydrolyzable ester group;
 R⁷ represents OH, NH₂, NHR⁵, or NR⁵₂; and

R⁵ is as described in claim 1;
pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof;
provided that those compounds of the above formula III are excluded wherein
B is adenine, xanthine, hypoxanthine, guanine, 2-aminopurine, 2,6-diaminopurine, cytosine, thymine, or uracil,
X is alk₂-Q¹ wherein alk₂ is selected from a chemical bond or C₁-C₄ alkylene, Q¹ is hydrogen or hydroxyl, and
R¹ and R⁷ are OH, unsubstituted C₄-C₆ alkoxy, phenoxy or phenyl-C₁-C₄ alkoxy.

4. The compound of claim 1 which has the general structural formula IV

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15



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FORMULA IV

wherein

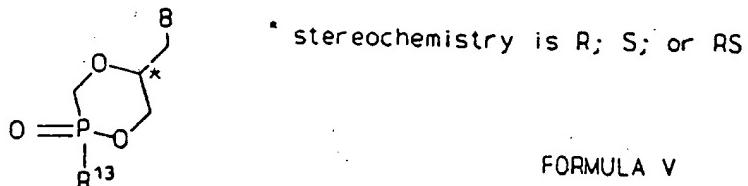
25

R⁸ and R⁹ are identical or different and independently of one another are each NR¹², or oxygen;
R¹⁰ and R¹¹ are identical or different and independently of one another are each hydrogen, or R⁵;
R¹² represents hydrogen or a lower alkyl;
m and n are identical or different and independently of one another are each 0 or 1;
30 R and R⁵ are as described in claim 1; and
X is as described in claim 2.

5. The compound which has the general structural formula V

35

40



FORMULA V

45

wherein

45

R¹³ represents OR⁴, NHR⁵, NR⁵₂, or OH, provided that R¹³ is not OH when B is A or C; and
B, R⁴, and R⁵ are as described in claim 1;
pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

- 50 6. The compound of claim 1, wherein R⁴ is C₄-C₂₀ alkyl, aryl or aryl-alkyl which may be unsubstituted or substituted by substituents independently selected from hydroxy and halogen.
7. The compound of claim 1 wherein R¹ and R² are OR⁴, and R⁴ represents a physiologically hydrolyzable ester group selected from CH₂OC(O)R⁵; and CH(R⁵)OC(O)R⁵ (R;S; or R S stereochemistry); or aryl wherein aryl is substituted by substituents independently selected from hydroxy and halogen.
- 55 8. The compound of claim 1 which is

- PMEA, di-(propionyloxymethyl ester);
PMEA, di-(isobutyryloxymethyl ester);
PMEA, bis-diethylamide;
PMEA, di-(butylacetate ester);
PMEA, di-(ethylacetate ester);
PMEA, di-(benzoyloxymethyl ester);
PMEA, dibutylamide;
PMEA, di-(2-methylpropyl ester); or
PMEA, di-(3-methylbutyl ester).
- 10 9. The compound of claim 1 which is
PMEA, di-(pivaloyloxymethyl ester).
- 15 10. The compound of claim 3 which is
PMEA, mono-(pivaloyloxymethyl ester);
PMEA, mono-(octyl ester);
PMEA, mono-(hydroxy-2,2-dimethylpropyl ester);
20 PMEA, mono-(2,2,2-trichloroethyl ester); or
PMEA, mono-(2,2-difluoro-3-hydroxypropyl ester).
11. The compound of claim 4 which is
25 PMEA, cyclic propanyl diester;
PMEA, cyclic (2,2-dimethyl)propanyl diester;
PMEA, cyclic (2,2-dimethyl)propanyl diamide;
PMEA, N,N-dimethyl-cyclic propanyl diamide.
- 30 12. The compound which is
PMEA, di-(isopropyl ester);
PMEHx, mono-(isopropyl ester);
6-chloro-9-(2-phosphonylmethoxy)ethylpurine,
35 di-(isopropyl ester);
9-(2-phosphonylmethoxy)ethylpurine, di-(isopropyl ester);
PMEA, mono-(isopropyl ester);
PMEA, (mono-isopropyl, mono-pivaloyloxymethyl) ester; or
40 PMEA, (mono-isopropyl, mono-phenyl) ester;
pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.
13. The compound which is
45 PMEA, di-(phenyl ester);
PMEA, di-(p-nitrobenzyl ester);
PMEA, di-(2,2,2-trichloroethyl ester);
PMEA, di-(p-trifluoromethylbenzyl ester);
PMEA, mono-(choline ester);
PMEA, (mono-N,N-diethylacetamide, mono-pivaloyloxymethyl) ester;
50 PMEA, mono-(3-hydroxypropanyl ester);
PMEA, mono-(3-amino-2,2-dimethylpropyl amide);
PMEA, mono-(N,N-diethylacetamide ester);
PMEA, mono-(acetic acid ester);
PMEA, mono-(N,N-diisopropylacetamide ester);
55 PMEA, mono-(p-nitrobenzyl ester); or
PMEA, mono-(p-trifluoromethylbenzyl ester);
PMEA, mono-(phenyl ester);
pharmaceutically acceptable acid addition salts, metal salts, and solvates thereof.

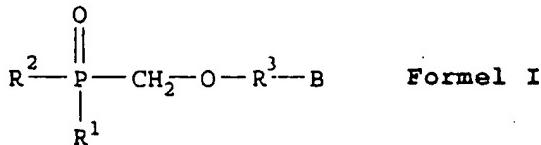
- 14. A process for producing the compound of claim 1, 2, 12, or 13 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide; or hydrolysis of the diethers or diamines.
- 5 15. A process for producing the compound of claim 3, 12, or 13 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or hydrolysis of the diethers or diamines.
- 16. A process for producing the compound of claim 4 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol.
- 10 17. A process for producing the compound of claim 5 which comprises reacting the phosphonate with an activating agent, then reacting with the appropriate amine or alcohol; or alkylation of the phosphonate with the appropriate alkyl halide.
- 15 18. The use of a compound as defined in anyone of claims 1 to 13 for preparing a pharmaceutical composition for the treatment of viral infection in a mammal.
- 19. The use of a compound as defined in anyone of claims 1 to 13 for preparing a pharmaceutical composition for inhibiting growth of a tumor in a mammal.
- 20 20. A process for preparing a pharmaceutical composition which comprises mixing an amount of at least one compound as defined in anyone of claims 1 to 13 with a pharmaceutically acceptable substantially nontoxic carrier or excipient.

25 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

30 1. Verbindung mit der Strukturformel I

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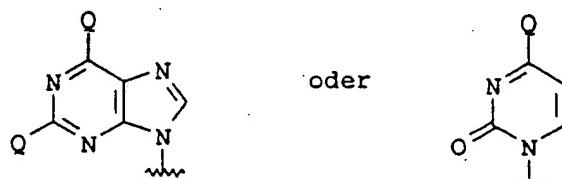


worin

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B für Adenin (A), Cytosin (C), Guanin (G), Thymin (T), Uracil (U), 2,6-Diaminopurin (DAP), Hypoxanthin (Hx) steht,

45



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worin

Q unabhängig ausgewählt ist aus H, Cl, NHR⁵, NR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH oder NCHN(R⁵)₂; R¹ und R² gleich oder verschieden sind und unabhängig voneinander jeweils für OR⁴, NH₂, NHR⁵ oder N(R⁵)₂ stehen; R¹ und R² gegebenenfalls miteinander unter Bildung einer cyclischen Gruppe verbunden sind oder R¹ oder R² gegebenenfalls mit R³ unter Bildung einer cyclischen Gruppe verbunden sind; R³ für C₁-C₂₀-Alkylen steht, das unsubstituiert oder mit unabhängig aus Hydroxy und Halogen ausgewählten

Substituenten substituiert ist; oder R³ für CH(CH₂OR⁶)CH₂ steht, wobei R¹ und R² jeweils unabhängig zusätzlich für OH stehen können und R⁶ eine hydrolyzierbare Estergruppe ist;

R⁴ für eine physiologisch hydrolyzierbare Estergruppe steht, die ausgewählt ist unter CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R; S; oder RS Stereochemie), CH₂C(R⁵)₂CH₂OH oder CH₂OR⁵; oder R⁴ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituiertes C₄-C₂₀-Alkyl, Aryl-Alkyl oder Aryl steht, mit der Maßgabe, daß R¹ und R² nicht gleichzeitig Alkoxy sind;

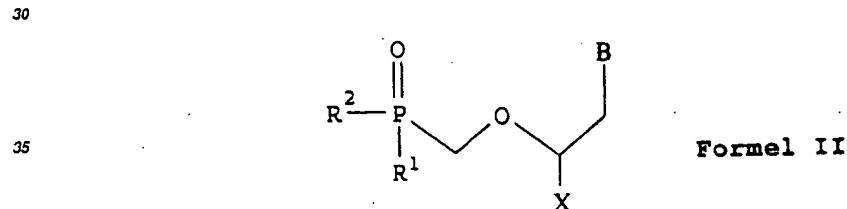
R⁵ für unsubstituierte oder durch unabhängig aus Hydroxy und Halogen ausgewählten Substituenten substituiertes C₁-C₂₀-Alkyl, Aryl oder Aryl-Alkyl steht;

pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon; mit der Maßgabe, daß diejenigen Verbindungen obiger Formel I ausgeschlossen sind, worin B für Adenin, Xanthin, Hypoxanthin, Guanin, 2-Aminopurin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil steht, R³ für



steht worin alk₁ an B gebunden ist, alk₁, alk₂ und alk₃ unabhängig voneinander ausgewählt sind unter einer chemischen Bindung oder C₁-C₄-Alkylen, R^a für Wasserstoff oder C₁-C₄-Alkyl und Q¹ für Wasserstoff oder Hydroxi steht und R¹ und R² für unsubstituiertes C₄-C₆-Alkoxy, Phenoxy oder Phenyl-C₁-C₄-Alkoxy stehen.

2. Verbindung nach Anspruch 1 mit der allgemeinen Strukturformel II



40 worin

B, R¹ und R² wie in Anspruch 1 definiert sind, mit der Maßgabe, daß R⁵ nicht CH₃ ist, falls Q für NCHN(R⁵)₂ steht;

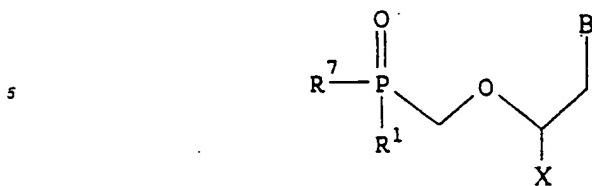
X für Wasserstoff, CH₂OR⁶ (R; S; oder RS Stereochemie), oder substituiertes oder unsubstituiertes Niedrigalkyl, insbesondere Methyl oder Hydroxymethyl steht; falls X für CH₂OR⁶ steht, R¹ und R² unabhängig zusätzlich OH sein können; und

R⁶ für eine hydrolyzierbare Estergruppe steht.

3. Verbindung mit der allgemeinen Strukturformel III

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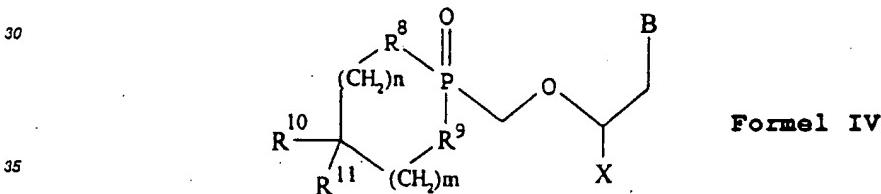
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10
worin

- B und R¹ wie zuvor in Anspruch 1 definiert sind;
 X für Wasserstoff, CH₂OR⁶ (R; S; oder RS Stereochemie), oder substituiertes oder unsubstituiertes Niedrigalkyl, insbesondere Methyl oder Hydroxymethyl steht; falls X für CH₂OR⁶ steht, R¹ zusätzlich OH sein kann; und R⁶ eine hydrolysierbare Estergruppe ist;
 R⁷ für OH, NH₂, NHR⁵ oder NR⁵₂ steht; und
 R⁵ wie in Anspruch 1 definiert ist; pharmazeutische akzeptable Säureadditionssalze, Metallsalze und Solvate davon;
 20 mit der Maßgabe, daß diejenigen Verbindungen obiger Formel III ausgeschlossen sind, worin
 B für Adenin, Xanthin, Hypoxanthin, Guanin, 2-Aminopurin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil steht,
 X für alk₂-Q¹ steht, worin alk₂ ausgewählt ist unter einer chemischen Bindung oder C₁-C₄-Alkylen, Q¹ für Was-
 serstoff oder Hydroxyl steht und R¹ und R⁷ für OH, unsubstituiertes C₄-C₆-Alkoxy, Phenoxy oder Phenyl-C₁-
 25 C₄-Alkoxy stehen.

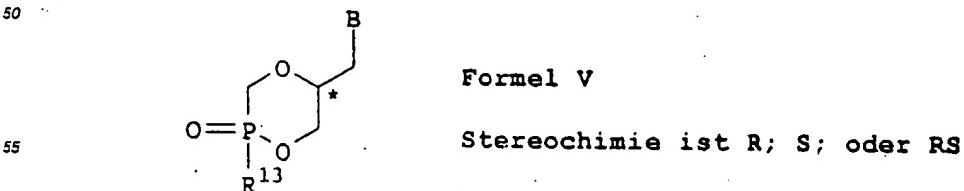
4. Verbindung nach Anspruch 1 mit der allgemeinen Strukturformel IV



worin

- R⁸ und R⁹ gleich oder verschieden sind und unabhängig voneinander jeweils für NR¹² oder Sauerstoff stehen;
 R¹⁰ und R¹¹ gleich oder verschieden sind und unabhängig voneinander jeweils für Wasserstoff oder R⁵ ste-
 hen;
 R¹² für Wasserstoff oder Niedrigalkyl steht;
 m und n gleich oder verschieden sind und unabhängig voneinander jeweils für 0 oder 1 stehen;
 45 B und R⁵ wie in Anspruch 1 definiert sind; und
 X wie in Anspruch 2 definiert ist.

5. Verbindung mit der allgemeinen Strukturformel V



worin

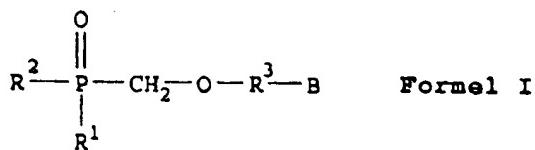
- 5 R¹³ für OR⁴, NHR⁵, NR⁵₂ oder OH steht, mit der Maßgabe, daß R¹³ nicht OH ist, falls B für A oder C steht; und
B, R⁴, und R⁵ wie in Anspruch 1 definiert sind;
pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon.
- 10 6. Verbindung nach Anspruch 1, worin R⁴ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituiertes C₄-C₂₀-Alkyl, Aryl oder Aryl-Alkyl steht.
- 15 7. Verbindung nach Anspruch 1, worin R¹ und R² für OR⁴ und R⁴ für eine aus CH₂OC(O)R⁵ und CH(R⁵)OC(O)R⁵ (R;
S; oder RS Stereochemie) ausgewählte, physiologisch hydrolysierbare Estergruppe oder Aryl steht, worin Aryl mit unabhängig aus Hydroxy und Halogen ausgewählten Substituenten substituiert ist.
- 20 8. Verbindung nach Anspruch 1, nämlich
PMEA, Di(propionyloxymethylester);
PMEA, Di(isobutyryloxymethylester);
PMEA, Bis(diethylamid);
PMEA, Di(butylacetatester);
PMEA, Di(ethylacetatester);
PMEA, Di(benzoyloxymethylester);
PMEA, Dibutylamid;
PMEA, Di(2-methylpropylester); oder
PMEA, Di(3-methylbutylester).
- 25 9. Verbindung nach Anspruch 1, nämlich
PMEA, Di(pivaloyloxymethylester).
- 30 10. Die Verbindung nach Anspruch 3, nämlich
PMEA, Mono(pivaloyloxymethylester);
PMEA, Mono(octylester);
PMEA, Mono(hydroxy-2,2-dimethylpropylester);
35 PMEA, Mono-(2,2,2-trichlorethylester); oder
PMEA, Mono-(2,2-difluor-3-hydroxypropylester).
- 40 11. Verbindung nach Anspruch 4, nämlich
PMEA, cyclischer Propanyldiester;
PMEA, cyclischer (2,2-Dimethyl)propanyldiester;
PMEA, cyclisches (2,2-Dimethyl)propanyldiamid;
PMEA, N,N'-Dimethyl-cyclisches Propanyldiamid.
- 45 12. Verbindung, nämlich
PMEA, Di(isopropylester);
PMEHx, Mono(isopropylester);
6-Chlor-9-(2-phosphonylmethoxy)ethylpurin,
50 Di(isopropylester);
9-(2-Phosphonylmethoxy)ethylpurin, Di(isopropylester);
PMEA, Mono(isopropylester);
PMEA, (Monoisopropyl, monopivaloyloxymethyl)ester; oder
PMEA, (Monoisopropyl, monophenyl)ester;
55 pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon.
13. Verbindung, nämlich

- 5
- PMEA, Di(phenylester);
 PMEA, Di-(p-nitrobenzylester);
 PMEA, Di-(2,2,2-trichlorethylester);
 PMEA, Di-(p-trifluormethylbenzylester);
 PMEA, Mono(cholinester);
 PMEA, (Mono-N,N-diethylacetamid, monopivaloyloxymethyl)ester;
 PMEA, Mono-(3-hydroxypropanylester);
 PMEA, Mono-(3-amino-2,2-dimethylpropylamid);
 10 PMEA, Mono-(N,N-diethylacetamide);
 PMEA, Mono(essigsäureester);
 PMEA, Mono-(N,N-diisopropylacetamide);
 PMEA, Mono-(p-nitrobenzylester); oder
 PMEA, Mono-(p-trifluormethylbenzylester);
 15 PMEA, Mono(phenylester);
 pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon.
- 20
14. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, 2, 12 oder 13, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder das Phosphonat mit dem geeigneten Alkylhalogenid alkyliert; oder die Diether oder Diamine hydrolysiert.
- 25
15. Verfahren zur Herstellung einer Verbindung nach Anspruch 3, 12 oder 13, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder die Diether oder Diamine hydrolysiert.
- 30
16. Verfahren zur Herstellung einer Verbindung nach Anspruch 4, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt.
17. Verfahren zur Herstellung einer Verbindung nach Anspruch 5, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder das Phosphonat mit dem geeigneten Alkylhalogenid alkyliert.
- 35
18. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung viraler Infektionen eines Säugers.
19. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung einer pharmazeutischen Zusammensetzung zur Wachstumshemmung eines Säugertumors.
- 40
20. Pharmazeutische Zusammensetzung mit wenigstens einer Verbindung der Ansprüche 1 bis 13 zusammen mit einem pharmazeutisch akzeptablen, im wesentlichen atoxischen Träger oder Excipienten.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung mit der Strukturformel I

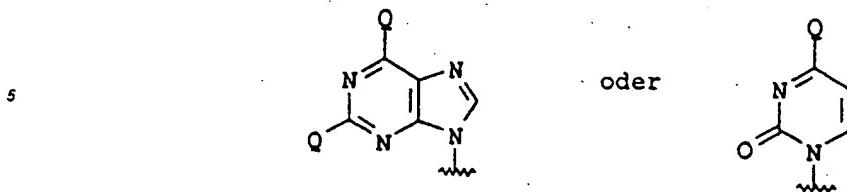
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worin

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B für Adenin (A), Cytosin (C), Guanin (G), Thymin (T), Uracil (U), 2,6-Diaminopurin (DAP), Hypoxanthin (Hx) steht.



worin

Q unabhängig ausgewählt ist aus H, Cl, NHR⁵, NR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH oder NCHN(R⁵)₂; R¹ und R² gleich oder verschieden sind und unabhängig voneinander jeweils für OR⁴, NH₂, NHR⁵ oder N(R⁵)₂ stehen; R¹ und R² gegebenenfalls miteinander unter Bildung einer cyclischen Gruppe verbunden sind oder R¹ oder R² gegebenenfalls mit R³ unter Bildung einer cyclischen Gruppe verbunden sind;

15 R³ für C₁-C₂₀-Alkylen steht, das unsubstituiert oder mit unabhängig aus Hydroxy und Halogen ausgewählten Substituenten substituiert ist; oder R³ für CH(CH₂OR⁶)CH₂ steht, wobei R¹ und R² jeweils unabhängig zusätzlich für OH stehen können und R⁶ eine hydrolysierbare Estergruppe ist;

20 R⁴ für eine physiologisch hydrolysierbare Estergruppe steht, die ausgewählt ist unter CH₂C(O)NR⁵, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R; S; oder RS Stereochemie), CH₂C(R⁵)₂CH₂OH oder CH₂OR⁵; oder R⁴ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substi-

tuenten substituiertes C₄-C₂₀-Alkyl, Aryl-Alkyl oder Aryl steht, mit der Maßgabe, daß R¹ und R² nicht gleich-

zeitig Alkoxy sind;

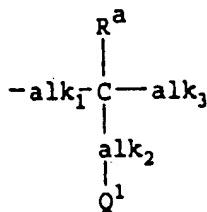
25 R⁵ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituierter C₁-C₂₀-Alkyl, Aryl oder Aryl-Alkyl steht;

pharmazeutisch akzeptabler Säureadditionssalze, Metallsalze und Solvate davon;

mit der Maßgabe, daß diejenigen Verbindungen obiger Formel I ausgeschlossen sind, worin

B für Adenin, Xanthin, Hypoxanthin, Guanin, 2-Aminopurin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil steht, R³ für

30

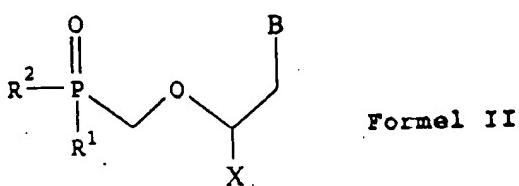


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steht worin alk₁ an B gebunden ist, alk₁, alk₂ und alk₃ unabhängig voneinander ausgewählt sind unter einer chemischen Bindung oder C₁-C₄-Alkylen, R^a für Wasserstoff oder C₁-C₄-Alkyl und Q¹ für Wasserstoff oder Hydroxyl steht und R¹ und R² für unsubstituiertes C₄-C₆-Alkoxy, Phenoxy oder Phenyl-C₁-C₄-Alkoxy stehen; wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder das Phosphonat mit dem geeigneten Alkyhalogenid alkyliert; oder die Diether oder Diamine hydrolysiert.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus Anspruch 1 mit der allgemeinen Strukturformel II

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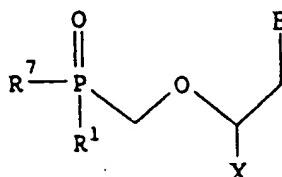


worin

B, R¹ und R² wie in Anspruch 1 definiert sind, mit der Maßgabe, daß R⁵ nicht CH₃ ist, falls Q für NCHN(R⁵)₂ steht;

X für Wasserstoff, CH₂OR⁶ (R; S; oder RS Stereochemie), oder substituiertes oder unsubstituiertes Niedrigalkyl, insbesondere Methyl oder Hydroxymethyl steht; falls X für CH₂OR⁶ steht, R¹ und R² unabhängig zusätzlich OH sein können; und R⁶ für eine hydrolysierbare Estergruppe steht.

10 3. Verfahren zur Herstellung einer Verbindung mit der allgemeinen Strukturformel III



Formel III

20

worin

B und R¹ wie zuvor in Anspruch 1 definiert sind;

X für Wasserstoff, CH₂OR⁶ (R; S; oder RS Stereochemie), oder substituiertes oder unsubstituiertes Niedrigalkyl, insbesondere Methyl oder Hydroxymethyl steht; falls X für CH₂OR⁶ steht, R¹ zusätzlich OH sein kann; und R⁶ eine hydrolysierbare Estergruppe ist;

R⁷ für OH, NH₂, NHR⁵ oder NR⁵₂ steht; und

R⁵ wie in Anspruch 1 definiert ist; pharmazeutische akzeptabla Säureadditionssalze, Metallsalze und Solvate davon;

mit der Maßgabe, daß diejenigen Verbindungen obiger Formel III ausgeschlossen sind, worin

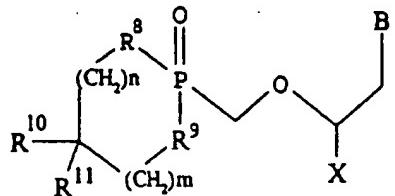
B für Adenin, Xanthin, Hypoxanthin, Guanin, 2-Aminopurin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil steht,

X für alk₂-Q¹ steht, worin alk₂ ausgewählt ist unter einer chemischen Bindung oder C₁-C₄-Alkylen, Q¹ für Wasserstoff oder Hydroxyl steht und R¹ und R⁷ für OH, unsubstituiertes C₄-C₆-Alkoxy, Phenoxy oder Phenyl-C₁-C₄-Alkoxy stehen;

wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder die Diether oder Diamine hydrolysiert.

40 4. Verfahren zur Herstellung einer Verbindung aus Anspruch 1 mit der allgemeinen Strukturformel IV

40



Formel IV

50

worin

R⁸ und R⁹ gleich oder verschieden sind und unabhängig voneinander jeweils für NR¹² oder Sauerstoff stehen; R¹⁰ und R¹¹ gleich oder verschieden sind und unabhängig voneinander jeweils für Wasserstoff oder R⁵ stehen;

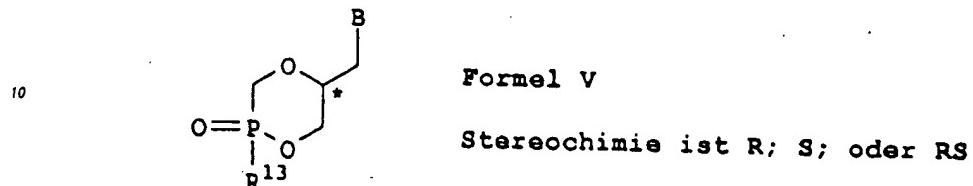
R¹² für Wasserstoff oder Niedrigalkyl steht;

m und n-gleich oder verschieden sind und unabhängig voneinander jeweils für 0 oder 1 stehen;

B und R⁵ wie in Anspruch 1 definiert sind; und

X wie in Anspruch 2 definiert ist;
wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt.

5. Verfahren zur Herstellung einer Verbindung mit der allgemeinen Strukturformel V



15
worin

R¹³ für OR⁴, NHR⁵, NR⁵₂ oder OH steht, mit der Maßgabe, daß R¹³ nicht OH ist, falls B für A oder C steht; und B, R⁴, und R⁵ wie in Anspruch 1 definiert sind; pharmazeutisch akzeptabler Säureadditionssalze, Metallsalze und Solvate davon;
wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder das Phosphonat mit dem geeigneten Alkyhalogenid alkaliert.

20
6. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus Anspruch 1, worin R⁴ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituiertes C₄-C₂₀-Alkyl, Aryl oder Aryl-Alkyl steht.

25
7. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus Anspruch 1, worin R¹ und R² für OR⁴ und R⁴ für eine aus CH₂OC(O)R⁵ und CH(R⁵)OC(O)R⁵ (R; S; oder RS Stereochemie) ausgewählte, physiologisch hydrolyzierbare Estergruppe oder Aryl steht, worin Aryl mit unabhängig aus Hydroxy und Halogen ausgewählten Substituenten substituiert ist.

30
8. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus Anspruch 1, nämlich

35
PMEA, Di(propionyloxymethylester);
PMEA, Di(isobutyryloxymethylester);
PMEA, Bis(diethylamid);
PMEA, Di(butylacetatester);
PMEA, Di(ethylacetatester);
40
PMEA, Di(benzoyloxymethylester);
PMEA, Dibutylamid;
PMEA, Di(2-methylpropylester); oder
PMEA, Di(3-methylbutylerster).

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9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus Anspruch 1, nämlich

PMEA, Di(pivaloyloxymethylester).

10. Verfahren nach Anspruch 3 zur Herstellung einer Verbindung aus Anspruch 3, nämlich

50
PMEA, Mono(pivaloyloxymethylester);
PMEA, Mono(octylester);
PMEA, Mono(hydroxy-2,2-dimethylpropylester);
PMEA, Mono-(2,2,2-trichlorethylester); oder
55
PMEA, Mono-(2,2-difluor-3-hydroxypropylester).

11. Verfahren nach Anspruch 4 zur Herstellung einer Verbindung aus Anspruch 4, nämlich

PMEA, cyclischer Propanyldiester;
 PMEA, cyclischer (2,2-Dimethyl)propanyldiester;
 PMEA, cyclisches (2,2-Dimethyl)propanyldiamid;
 PMEA, N,N'-Dimethyl-cyclisches Propanyldiamid.

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12. Verfahren nach Anspruch 1 oder Anspruch 3 zur Herstellung einer Verbindung, nämlich

PMEA, Di(isopropylester);
 PMEHx, Mono(isopropylester);
 10 6-Chlor-9-(2-phosphorylmethoxy)ethylpurin,
 Di(isopropylester);
 9-(2-Phosphorylmethoxy)ethylpurin, Di(isopropylester);
 PMEA, Mono(isopropylester);
 PMEA, (Monoisopropyl, monopivaloyloxymethyl)ester; oder
 15 PMEA, (Monoisopropyl, monophenyl)ester;
 pharmazeutisch akzeptabler Säureadditionssalze, Metallsalze und Solvate davon.

13. Verfahren nach Anspruch 1 oder Anspruch 3 zur Herstellung einer Verbindung, nämlich

20 PMEA, Di(phenylester);
 PMEA, Di-(p-nitrobenzylester);
 PMEA, Di-(2,2,2-trichlorethylester);
 PMEA, Di-(p-trifluormethylbenzylester);
 PMEA, Mono(cholinester);
 25 PMEA, (Mono-N,N-diethylacetamid, monopivaloyloxymethyl)ester;
 PMEA, Mono-(3-hydroxypropanylester);
 PMEA, Mono-(3-amino-2,2-dimethylpropylamid);
 PMEA, Mono-(N,N-diethylacetamidester);
 PMEA, Mono(essigsäureester);
 30 PMEA, Mono-(N,N-diisopropylacetamidester);
 PMEA, Mono-(p-nitrobenzylester); oder
 PMEA, Mono-(p-trifluormethylbenzylester);
 PMEA, Mono(phenylester);
 pharmazeutisch akzeptabler Säureadditionssalze, Metallsalze und Solvate davon.

35

14. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung viraler Infektionen eines Säugers.

15. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung einer pharmazeutischen Zusammensetzung zur Wachstumshemmung eines Säugertumors.

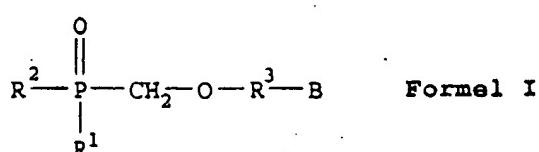
16. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wobei man eine Menge wenigstens einer in einem der Ansprüche 1 bis 13 definierten Verbindung mit einem pharmazeutisch akzeptablen, im wesentlichen atoxischen Träger oder Excipienten mischt.

45

Patentansprüche für folgenden Vertragsstaat : GR

1. Verbindung mit der Strukturformel I

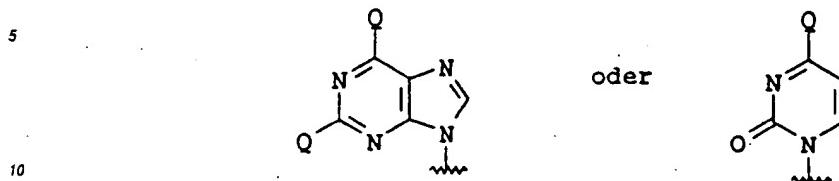
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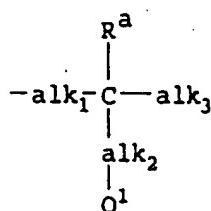
warin

B für Adenin (A), Cytosin (C), Guanin (G), Thymin (T), Uracil (U), 2,6-Diaminopurin (DAP), Hypoxanthin (Hx) steht,



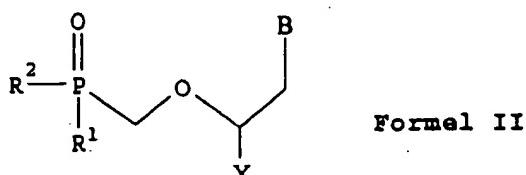
worin

Q unabhängig ausgewählt ist aus H, Cl, NHR⁵, NR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH oder NCHN(R⁵)₂; R¹ und R² gleich oder verschieden sind und unabhängig voneinander jeweils für OR⁴, NH₂, NHR⁵ oder N(R⁵)₂ stehen; R¹ und R² gegebenenfalls miteinander unter Bildung einer cyclischen Gruppe verbunden sind oder R¹ oder R² gegebenenfalls mit R³ unter Bildung einer cyclischen Gruppe verbunden sind; R³ für C₁-C₂₀-Alkylen steht, das unsubstituiert oder mit unabhängig aus Hydroxy und Halogen ausgewählten Substituenten substituiert ist; oder R³ für CH(CH₂OR⁶)CH₂ steht, wobei R¹ und R² jeweils unabhängig zusätzlich für OH stehen können und R⁶ eine hydrolyzierbare Estergruppe ist; R⁴ für eine physiologisch hydrolyzierbare Estergruppe steht, die ausgewählt ist unter CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (R; S; oder RS Stereochemie), CH₂C(R⁵)₂CH₂OH oder CH₂OR⁵; oder R⁴ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituiertes C₄-C₂₀-Alkyl, Aryl-Alkyl oder Aryl steht, mit der Maßgabe, daß R¹ und R² nicht gleichzeitig Alkoxy sind; R⁵ für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituiertes C₁-C₂₀-Alkyl, Aryl oder Aryl-Alkyl steht; pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon; mit der Maßgabe, daß diejenigen Verbindungen obiger Formel I ausgeschlossen sind, worin B für Adenin, Xanthin, Hypoxanthin, Guanin, 2-Aminopurin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil steht, R³ für



steht worin alk₁ an B gebunden ist, alk₁, alk₂ und alk₃ unabhängig voneinander ausgewählt sind unter einer chemischen Bindung oder C₁-C₄-Alkylen, R^a für Wasserstoff oder C₁-C₄-Alkyl und Q¹ für Wasserstoff oder Hydroxyl steht und R¹ und R² für unsubstituiertes C₄-C₆-Alkoxy, Phenoxy oder Phenyl-C₁-C₄-Alkoxy stehen.

2. Verbindung nach Anspruch 1 mit der allgemeinen Strukturformel II



worin

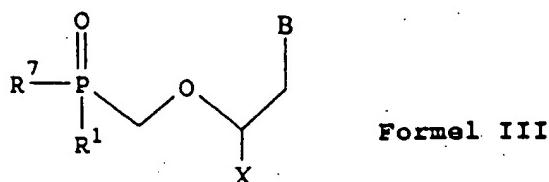
B, R¹ und R² wie in Anspruch 1 definiert sind, mit der Maßgabe, daß R⁵ nicht CH₃ ist, falls Q für NCHN(R⁵)₂ steht;

X für Wasserstoff, CH₂OR⁶ (R; S; oder RS Stereochemie), oder substituiertes oder unsubstituiertes Niedrigalkyl, insbesondere Methyl oder Hydroxymethyl steht; falls X für CH₂OR⁶ steht, R¹ und R² unabhängig zusätzlich OH sein können; und

R⁶ für eine hydrolysierbare Estergruppe steht.

3. Verbindung mit der allgemeinen Strukturformel III

10



15

worin

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B und R¹ wie zuvor in Anspruch 1 definiert sind;

X für Wasserstoff, CH₂OR⁶ (R; S; oder RS Stereochemie), oder substituiertes oder unsubstituiertes Niedrigalkyl, insbesondere Methyl oder Hydroxymethyl steht; falls X für CH₂OR⁶ steht, R¹ zusätzlich OH sein kann; und R⁶ eine hydrolysierbare Estergruppe ist;

25

R⁷ für OH, NH₂, NHR⁵ oder NR⁵₂ steht; und

R⁵ wie in Anspruch 1 definiert ist;

pharmazeutische akzeptable Säureadditionssalze, Metallsalze und Solvate davon;

mit der Maßgabe, daß diejenigen Verbindungen obiger Formel III ausgeschlossen sind, worin

30

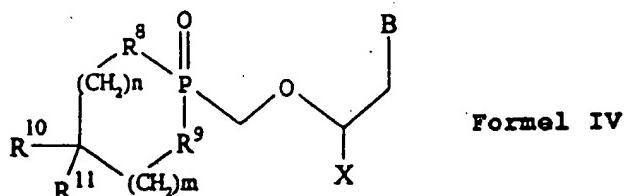
B für Adenin, Xanthin, Hypoxanthin, Guanin, 2-Aminopurin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil steht,

X für alk₂Q¹ steht, worin alk₂ ausgewählt ist unter einer chemischen Bindung oder C₁-C₄-Alkylen, Q¹ für Wasserstoff oder Hydroxyl steht und R¹ und R⁷ für OH, unsubstituiertes C₄-C₆-Alkoxy, Phenoxy oder Phenyl-C₁-C₄-Alkoxy stehen.

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4. Verbindung nach Anspruch 1 mit der allgemeinen Strukturformel IV

40



45

worin

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R⁸ und R⁹ gleich oder verschieden sind und unabhängig voneinander jeweils für NR¹² oder Sauerstoff stehen;

R¹⁰ und R¹¹ gleich oder verschieden sind und unabhängig voneinander jeweils für Wasserstoff oder R⁵ stehen;

R¹² für Wasserstoff oder Niedrigalkyl steht;

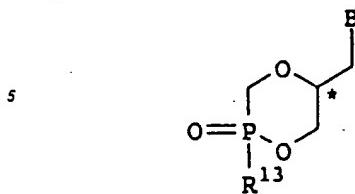
m und n gleich oder verschieden sind und unabhängig voneinander jeweils für 0 oder 1 stehen;

B und R⁵ wie in Anspruch 1 definiert sind; und

X wie in Anspruch 2 definiert ist.

55

5. Verbindung mit der allgemeinen Strukturformel V



Formel V

Stereochimie ist R; S; oder RS

10

worin

15 R^{13} für OR^4 , NHR^5 , NR^5_2 oder OH steht, mit der Maßgabe, daß R^{13} nicht OH ist, falls B für A oder C steht; und
 B , R^4 , und R^5 wie in Anspruch 1 definiert sind;
pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon.

- 20 6. Verbindung nach Anspruch 1, worin R^4 für unsubstituiertes oder durch unabhängig aus Hydroxy und Halogen ausgewählte Substituenten substituiertes C_4 - C_{20} -Alkyl, Aryl oder Aryl-Alkyl steht.
7. Verbindung nach Anspruch 1, worin R^1 und R^2 für OR^4 und R^4 für eine aus $CH_2OC(O)R^5$ und $CH(R^5)OC(O)R^5$ (R ; S; oder RS Stereochemie) ausgewählte, physiologisch hydrolysierbare Estergruppe oder Aryl steht, worin Aryl mit unabhängig aus Hydroxy und Halogen ausgewählten Substituenten substituiert ist.
- 25 8. Verbindung nach Anspruch 1, nämlich

PMEA, Di(propionyloxymethylester);
PMEA, Di(isobutyryloxymethylester);
PMEA, Bis(diethylamid);
30 PMEA, Di(butylacetatester);
PMEA, Di(ethylacetatester);
PMEA, Di(benzoyloxymethylester);
PMEA, Dibutylamid;
PMEA, Di(2-methylpropylester); oder
35 PMEA, Di(3-methylbutylester).

9. Verbindung nach Anspruch 1, nämlich

PMEA, Di(pivaloyloxymethylester).

- 40 10. Die Verbindung nach Anspruch 3, nämlich

PMEA, Mono(pivaloyloxymethylester);
PMEA, Mono(octylester);
45 PMEA, Mono(hydroxy-2,2-dimethylpropylester);
PMEA, Mono-(2,2,2-trichlorethylester); oder
PMEA, Mono-(2,2-difluor-3-hydroxypropylester).

11. Verbindung nach Anspruch 4, nämlich

50 PMEA, cyclischer Propanyldiester;
PMEA, cyclischer (2,2-Dimethyl)propanyldiester;
PMEA, cyclisches (2,2-Dimethyl)propanyldiamid;
PMEA, N,N'-Dimethyl-cyclisches Propanyldiamid.

- 55 12. Verbindung, nämlich

PMEA, Di(isopropylester);

PMEHx, Mono(isopropylester);
6-Chlor-9-(2-phosphonylmethoxy)ethylpurin,
Di(isopropylester);
9-(2-Phosphonylmethoxy)ethylpurin, Di(isopropylester);
5 PMEA, Mono(isopropylester);
PMEA, (Monoisopropyl, monopivaloyloxymethyl)ester; oder
PMEA, (Monoisopropyl, monophenyl)ester;
pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon.

10 13. Verbindung, nämlich

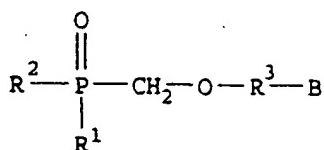
PMEA, Di(phenylester);
PMEA, Di-(p-nitrobenzylester);
PMEA, Di-(2,2,2-trichlorethylester);
15 PMEA, Di-(p-trifluormethylbenzylester);
PMEA, Mono(cholinester);
PMEA, (Mono-N,N-diethylacetamid, monopivaloyloxymethyl)ester;
PMEA, Mono-(3-hydroxypropyl)ester;
PMEA, Mono-(3-amino-2,2-dimethylpropylamid);
20 PMEA, Mono-(N,N-diethylacetamide);
PMEA, Mono(essigsäureester);
PMEA, Mono-(N,N-diisopropylacetamide);
PMEA, Mono-(p-nitrobenzylester); oder
25 PMEA, Mono-(p-trifluormethylbenzylester);
PMEA, Mono(phenylester);
pharmazeutisch akzeptable Säureadditionssalze, Metallsalze und Solvate davon,

14. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, 2, 12 oder 13, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder das Phosphonat mit dem geeigneten Alkylhalogenid alkyliert; oder die Diether oder Diamine hydrolysiert.
30 15. Verfahren zur Herstellung einer Verbindung nach Anspruch 3, 12 oder 13, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder die Diether oder Diamine hydrolysiert.
35 16. Verfahren zur Herstellung einer Verbindung nach Anspruch 4, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt.
17. Verfahren zur Herstellung einer Verbindung nach Anspruch 5, wobei man das Phosphonat mit einem Aktivierungsmittel und dann mit dem geeigneten Amin oder Alkohol umsetzt; oder das Phosphonat mit dem geeigneten Alkylhalogenid alkyliert.
40 18. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung viraler Infektionen eines Säugers.
45 19. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung einer pharmazeutischen Zusammensetzung zur Wachstumshemmung eines Säugertumors.
20. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wobei man eine Menge wenigstens einer in einem der Ansprüche 1 bis 13 definierten Verbindung mit einem pharmazeutisch akzeptablen, im wesentlichen atoxischen Träger oder Excipienten mischt.
50

Revendications

55 Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé ayant la formule développée I :



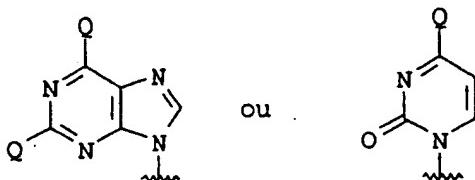
FORMULE I

10 dans laquelle

B représente l'adénine (A), la cytosine (C), la guanine (G), la thymine (T), l'uracile (U), la 2,6-diaminopurine (DAP), l'hypoxanthine (Hx);

15

20



25

dans laquelle

Q est indépendamment choisi parmi H, Cl, NHR⁵, NHR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH ou NCHN(R⁵)₂;

30

R¹ et R² sont identiques ou différents et représentent indépendamment OR⁴, NH₂, NHR⁵ ou N(R⁵)₂; R¹ et R² étant éventuellement liés l'un à l'autre pour former un groupe cyclique, ou R¹ ou R² étant éventuellement liés à R³ pour former un groupe cyclique;

35

R³ représente un groupe alkylène en C₁ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène; ou R³ représente CH(CH₂OR⁶)CH₂, auquel cas R¹ et R² peuvent en outre représenter indépendamment OH, et R⁶ représente un groupe ester hydrolysable;

40

R⁴ représente un groupe ester physiologiquement hydrolysable choisi parmi CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (stéréochimie R; S; ou RS), CH₂C(R⁵)₂CH₂OH, ou CH₂OR⁵; ou R⁴ représente un groupe alkyle, arylalkyle ou aryle en C₄ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène à condition que R¹ et R² ne représentent pas simultanément le groupe alkoxy;

45

R⁵ représente un groupe alkyle, aryle ou arylalkyle en C₁ à C₂₀ qui peut être substitué ou non substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène;

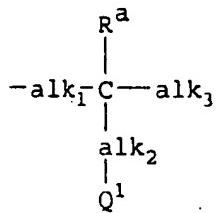
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci; à condition que soient exclus les composés de la formule I ci-dessus dans lesquels :

50

B représente l'adénine, la xanthine, l'hypoxanthine, la guanine, la 2-aminopurine, la 2,6-diaminopurine, la cytosine, la thymine, ou l'uracile,

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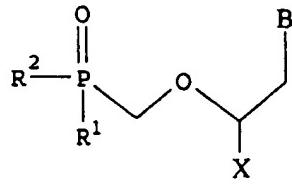
 R^3 représente

où alk_1 est lié à B, alk_1 , alk_2 et alk_3 sont indépendamment choisis parmi une liaison chimique ou un groupe alkylène en C_1 à C_4 , R^a représente l'hydrogène ou un groupe alkyle en C_1 à C_4 et Q^1 représente l'hydrogène ou un groupe hydroxyle, et R^1 et R^2 représentent des groupes alkoxy en C_4 à C_6 , phénoxy ou phénol-(C_1 à C_4)-alkoxy non substitués.

20

2. Composé selon la revendication 1 qui a la formule développée générale II :

25



FORMULE II

30

dans laquelle

35

B, R^1 et R^2 sont tels que décrits dans la revendication 1, à condition que lorsque Q représente $NCHN(R^5)_2$, alors R^5 ne représente pas CH_3 ;

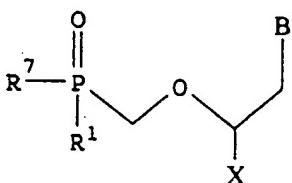
40

X représente l'hydrogène, CH_2OR^6 (stéréochimie R; S; ou RS), ou un groupe alkyle inférieur substitué ou non substitué, en particulier le groupe méthyle ou hydroxyméthyle; lorsque X représente CH_2OR^6 , R^1 et R^2 peuvent en outre être indépendamment choisis parmi OH; et

R^6 représente un groupe ester hydrolysable.

3. Composé ayant la formule développée générale III :

45



FORMULE III

50

dans laquelle

55

B, et R^1 sont tels que précédemment décrits dans la revendication 1;

X représente l'hydrogène, CH_2OR^6 (stéréochimie R; S; ou RS) ou un groupe alkyle inférieur substitué ou non

substitué; en particulier le groupe méthyle ou hydroxyméthyle; lorsque X représente CH_2OR^6 , R^1 peut en outre représenter OH; et R^6 représente un groupe ester hydrolysable;

R^7 représente OH, NH₂, NHR⁵, ou NR⁵₂; et

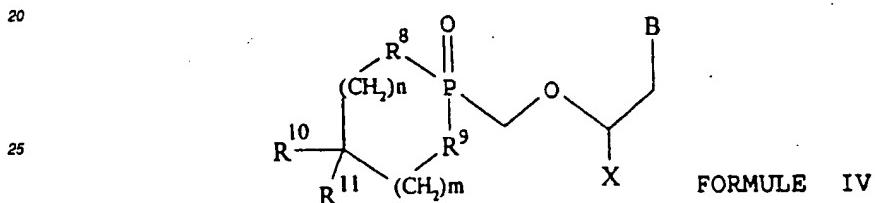
R⁵ est tel que décrit dans la revendication 1; sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci;

à condition que soient exclus les composés de la formule III ci-dessus dans laquelle :

10 B représente l'adénine, la xanthine, l'hypoxanthine, la guanine, la 2-aminopurine, la 2,6-diaminopurine, la cytosine, la thymine, ou l'uracile,

X représente alk₂-Q¹
où alk₂ est choisi parmi une liaison chimique ou un groupe alkylène en C₁ à C₄, Q¹ représente l'hydrogène ou le groupe hydroxyle, et R¹ et R⁷ représentent OH, un groupe alkoxy en C₄ à C₆, phénoxy ou phényl-(C₁ à C₄)-alcoxy non substitué.

4. Composé selon la revendication 1 qui a la formule développée générale IV :



30 dans laquelle

R⁸ et R⁹ sont identiques ou différents et représentent indépendamment NR¹², ou l'oxygène;

R^{10} et R^{11} sont identiques ou différents et représentent indépendamment l'hydrogène, ou R^5 ;

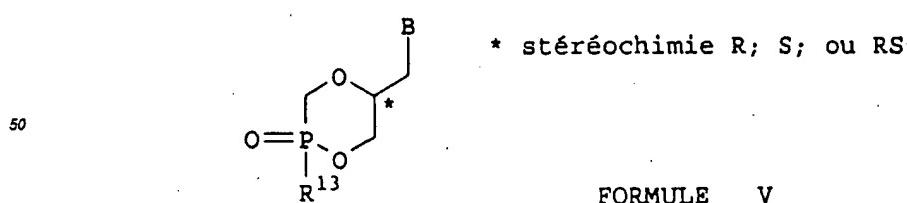
R^{12} représente l'hydrogène ou un groupe alkyle inférieur;

m et n sont identiques ou différents et représentent indépendamment 0 ou 1;

40 B et R⁵ sont tels que décrits dans la revendication 1; et

X est tel que décrit dans la revendication 2.

5. Composé qui a la formule développée générale V :



55

R¹³ représente CP4, NH₅, NS₅ ou OH à condition que R¹³ ne représente pas OH lorsque R représente A.

ou C; et

B, R⁴, et R⁵ sont tels que décrits dans la revendication 1;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

- 5 6. Composé selon la revendication 1, dans lequel R⁴ représente un groupe alkyle, aryle ou aryl-alkyle en C₄ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi les groupes hydroxy et halogène.
- 10 7. Composé selon la revendication 1 dans lequel R¹ et R² représentent OR⁴, et R⁴ représente un groupe ester physiologiquement hydrolysable choisi parmi CH₂OC(O)R⁵ et CH(R⁵)OC(O)R⁵ (stéréochimie R; S; ou RS); ou le groupe aryle dans lequel le groupe aryle est substitué par des substituants indépendamment choisis parmi les groupes hydroxy et halogène.
- 15 8. Composé selon la revendication 1 qui est
 di-(ester propionyloxyméthylique) de PMEA;
 di-(ester isobutyryloxyméthylique) de PMEA;
 bis-diéthylamide de PMEA;
 di-(ester acétate de butyle) de PMEA;
 25 di-(ester acétate d'éthyle) de PMEA;
 di-(ester benzoyloxyméthylique) de PMEA;
 dibutylamide de PMEA;
 30 di-(ester 2-méthylpropylque) de PMEA; ou
 di-(ester 3-méthylbutylique) de PMEA.
- 35 9. Composé selon la revendication 1 qui est
 di-(ester pivaloyloxyméthylique) de PMEA.
- 40 10. Composé selon la revendication 3 qui est
 mono-(ester pivaloyloxyméthylique) de PMEA;
 mono-(ester octylque) de PMEA;
 45 mono-(ester hydroxy-2,2-diméthylpropylque) de PMEA;
 mono-(ester 2,2,2-trichloroéthylque) de PMEA; ou
 mono-(ester 2,2-difluoro-3-hydroxypropylque) de PMEA.
- 50 11. Composé selon la revendication 4 qui est
 diester cyclopropanylque de PMEA;
 55 diester (2,2-diméthyl)cyclopropanylque de PMEA;
 diamide (2,2-diméthyl)cyclopropanylque de PMEA

diamide N,N'-diméthyl-cyclopropanylique de PMEA.

12. Composé qui est

5 di-(ester isopropylique) de PMEA;

mono-(ester isopropylique) de PMEHx;

10 di-(ester isopropylique) de 6-chloro-9-(2-phosphonylméthoxy)éthylpurine;

di-(ester isopropylique) de 9-(2-phosphonylméthoxy)éthylpurine;

mono-(ester isopropylique) de PMEA;

15 ester (mono-isopropylique, mono-pivaloyloxyméthylique) de PMEA; ou

ester (mono-isopropylique, mono-phénylique) de PMEA;

sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

20 13. Composé qui est

di-(ester phénylique) de PMEA;

25 di-(ester p-nitrobenzylique) de PMEA;

di-(ester 2,2,2-trichloroéthylique) de PMEA;

di-(ester p-trifluorométhylbenzylique) de PMEA;

30 mono-(ester cholinique) de PMEA;

ester (mono-N,N-diéthylacétamidique, mono-pvaloyloxyméthylique) de PMEA;

mono-(ester 3-hydroxypropanylique) de PMEA;

35 mono-(3-amino-2,2-diméthylpropylamide) de PMEA;

mono-(ester N,N-diéthylacétamidique) de PMEA;

40 mono-(ester de l'acide acétique) de PMEA;

mono-(ester N,N-diisopropylacétamidique) de PMEA;

45 mono-(ester p-nitrobenzylique) de PMEA; ou

mono-(ester p-trifluorométhylbenzylique) de PMEA;

mono-(ester phénylique) de PMEA;

sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

50 14. Procédé de production du composé selon la revendication 1, 2, 12 ou 13 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'alkylation du phosphonate avec l'halogénure d'alkyle approprié; ou l'hydrolyse des diéthers ou des diamines.

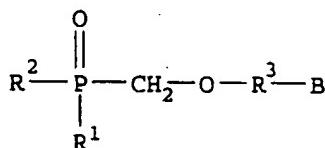
55 15. Procédé de production du composé selon la revendication 3, 12 ou 13 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'hydrolyse des diéthers ou des diamines.

16. Procédé de production du composé selon la revendication 4 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié.
17. Procédé de production du composé selon la revendication 5 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'alkylation du phosphonate avec l'halogénéure d'alkyle approprié.
18. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 13 pour préparer une composition pharmaceutique pour le traitement d'une infection virale chez un mammifère.
19. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 13 pour préparer une composition pharmaceutique pour inhiber la croissance d'une tumeur chez un mammifère.
20. Composition pharmaceutique qui comprend au moins un composé selon les revendications 1 à 13 associé avec un vecteur ou un excipient sensiblement non toxique pharmaceutiquement acceptable.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de production d'un composé ayant la formule développée I :

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FORMULE I

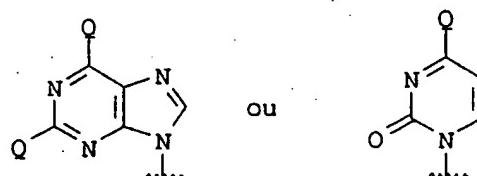
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dans laquelle

B représente l'adénine (A), la cytosine (C), la guanine (G); la thymine (T), l'uracile (U), la 2,6-diaminopurine (DAP), l'hypoxanthine (Hx).

35

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Q est indépendamment choisi parmi H, Cl, NHR⁵, NHR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH ou NCHN(R⁵)₂;

50

R¹ et R² sont identiques ou différents et représentent indépendamment OR⁴, NH₂, NHR⁵ ou N(R⁵)₂; R¹ et R² étant éventuellement liés l'un à l'autre pour former un groupe cyclique, ou R¹ ou R² étant éventuellement liés à R³ pour former un groupe cyclique;

55

R³ représente un groupe alkylène en C₁ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène; ou R³ représente CH(CH₂OR⁶)CH₂, auquel cas R¹ et R² peuvent en outre représenter indépendamment OH, et R⁶ représente un groupe ester hydrolysable;

R⁴ représente un groupe ester physiologiquement hydrolysable choisi parmi CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (stéréochimie R; S; ou RS), CH₂C(R⁵)₂CH₂OH, ou CH₂OR⁵; ou R⁴ repré-

sente un groupe alkyle, arylalkyle ou aryle en C₄ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène à condition que R¹ et R² ne représentent pas simultanément le groupe alkoxy;

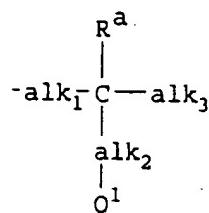
R⁵ représente un groupe alkyle, aryle ou arylalkyle en C₁ à C₂₀ qui peut être substitué ou non substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène;

sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci; à condition que soient exclus les composés de la formule I ci-dessus dans lesquels :

B représente l'adénine, la xanthine, l'hypoxanthine, la guanine, la 2-aminopurine, la 2,6-diaminopurine, la cytosine, la thymine, ou l'uracile,

R³ représente

15



25

où alk₁ est lié à B, alk₁, alk₂ et alk₃ sont indépendamment choisis parmi une liaison chimique ou un groupe alkylène en C₁ à C₄, R⁴ représente l'hydrogène ou un groupe alkyle en C₁ à C₄ et Q¹ représente l'hydrogène ou un groupe hydroxyle, et R¹ et R² représentent des groupes alkoxy en C₄ à C₆, phénoxy ou phényl-(C₁ à C₄)-alkoxy non substitués.

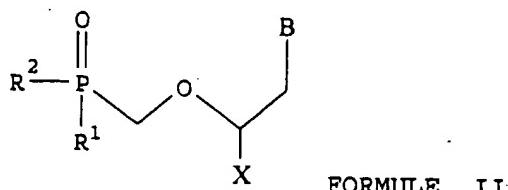
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lequel procédé comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'alkylation du phosphonate avec l'halogénure d'alkyle approprié; ou l'hydrolyse des diéthers ou des diamines.

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2. Procédé selon la revendication 1 pour produire un composé selon la revendication 1 qui a la formule développée générale II :

40



45

dans laquelle

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B, R¹ et R² sont tels que décrits dans la revendication 1, à condition que lorsque Q représente NCHN(R⁵)₂, alors R⁵ ne représente pas CH₃;

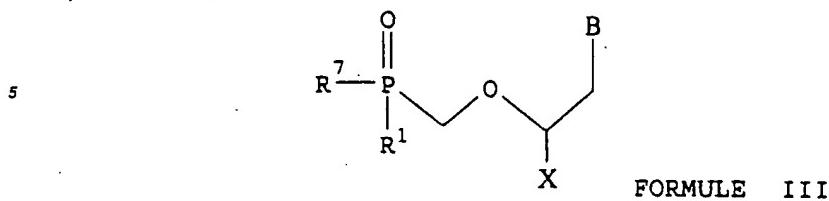
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X représente l'hydrogène, CH₂OR⁶ (stéréochimie R; S; ou RS), ou un groupe alkyle inférieur substitué ou non substitué, en particulier le groupe méthyle ou hydroxyméthyle; lorsque X représente CH₂OR⁶, R¹ et R² peuvent en outre être indépendamment choisis parmi OH; et

60

R⁶ représente un groupe ester hydrolysable.

3. Procédé de production d'un composé ayant la formule développée générale III :



10 dans laquelle

B, et R¹ sont tels que précédemment décrits dans la revendication 1;

15 X représente l'hydrogène, CH₂OR⁶ (stéréochimie R; S; ou RS) ou un groupe alkyle inférieur substitué ou non substitué, en particulier le groupe méthyle ou hydroxyméthyle; lorsque X représente CH₂OR⁶, R¹ peut en outre représenter OH; et R⁶ représente un groupe ester hydrolysable;

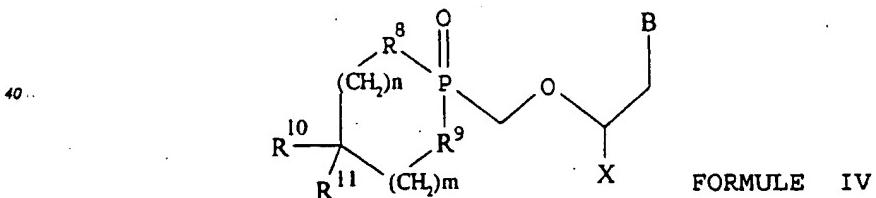
20 R⁷ représente OH, NH₂, NHR⁵, ou NR⁵₂; et

25 R⁵ est tel que décrit dans la revendication 1;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci;
à condition que soient exclus les composés de la formule III ci-dessus dans laquelle :

30 B représente l'adénine, la xanthine, l'hypoxanthine, la guanine, la 2-aminopurine, la 2,6-diaminopurine, la cytosine, la thymine, ou l'uracile,

35 X représente alk₂-Q¹
où alk₂ est choisi parmi une liaison chimique ou un groupe alkylène en C₁ à C₄, Q¹ représente l'hydrogène ou le groupe hydroxyle, et R¹ et R⁷ représentent OH, un groupe alkoxy en C₄ à C₆, phénoxy ou phényl-(C₁ à C₄)-alkoxy non substitué.
lequel procédé comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'hydrolyse des diéthers ou des diamines.

40 4. Procédé de production d'un composé selon la revendication 1 qui a la formule développée générale IV :



dans laquelle

50 R⁸ et R⁹ sont identiques ou différents et représentent indépendamment NR¹², ou l'oxygène;

R¹⁰ et R¹¹ sont identiques ou différents et représentent indépendamment l'hydrogène, ou R⁵;

R¹² représente l'hydrogène ou un groupe alkyle inférieur;

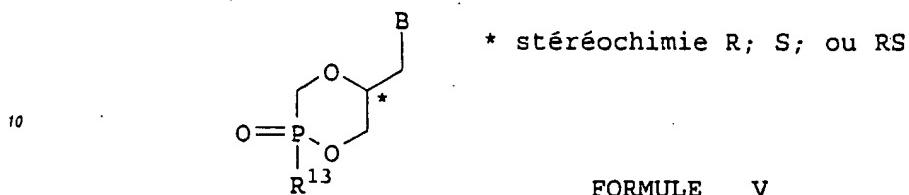
m et n sont identiques ou différents et représentent indépendamment 0 ou 1;

55 B et R⁵ sont tels que décrits dans la revendication 1; et

X est tel que décrit dans la revendication 2;

lequel procédé comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié.

- #### 5. Procédé de production d'un composé qui a la formule développée générale V :



15 dans laquelle

R^{13} représente OR^4 , NHR^5 , NR^5_2 , ou OH, à condition que R^{13} ne représente pas OH lorsque B représente A ou C; et

20 B, R⁴, et R⁵ sont tels que décrits dans la revendication 1;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci;
lequel procédé comprend la réaction du phosphonate avec un agent activant, puis la réaction avec
l'amine ou l'alcool approprié; ou l'alkylation du phosphonate avec l'halogénure d'alkyle approprié.

25 6. Procédé selon la revendication 1 pour produire un composé selon la revendication 1, dans lequel R⁴ représente un groupe alkyle, aryle ou aryl-alkyle en C₄ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi les groupes hydroxy et halogène.

30 7. Procédé selon la revendication 1 pour produire un composé selon la revendication 1 dans lequel R¹ et R² représentent OR⁴, et R⁴ représente un groupe ester physiologiquement hydrolysable choisi parmi CH₂OC(O)R⁵ et CH(R⁵)OC(O)R⁵ (stéréochimie R; S; ou RS); ou le groupe aryle dans lequel le groupe aryle est substitué par des substituants indépendamment choisis parmi les groupes hydroxy et halogène.

8. Procédé selon la revendication 1 pour produire un composé selon la revendication 1 qui est

35 di-(ester propionyloxyméthylique) de PMEA;

di-(ester isobutyryloxyméthylique) de PMEA;

40 bis-diéthylamide de PMEA;

di-(ester acétate de butyle)

di-(ester acétate d'éthyle) de PMEA:

di-(ester benzoyloxyméthylique) de B.

dibutamida de BMFA

ESTATE PLANNING

di-(ester pivaloyloxyméthylique) de PMEA.

10. Procédé selon la revendication 3 pour produire un composé selon la revendication 3 qui est

- mono-(ester pivaloyloxyméthylique) de PMEA;
- mono-(ester octylique) de PMEA;
- 5 mono-(ester hydroxy-2,2-diméthylpropylque) de PMEA;
- mono-(ester 2,2,2-trichloroéthylique) de PMEA; ou
- 10 mono-(ester 2,2-difluoro-3-hydroxypropylque) de PMEA.
11. Procédé selon la revendication 4 pour produire un composé selon la revendication 4 qui est
- diester cyclopropanylique de PMEA;
- 15 diester (2,2-diméthyl)cyclopropanylique de PMEA;
- diamide (2,2-diméthyl)cyclopropanylique de PMEA
- 20 diamide N,N'-diméthyl-cyclopropanylique de PMEA.
12. Procédé selon la revendication 1 ou la revendication 3 pour produire un composé qui est
- di-(ester isopropylique) de PMEA;
- 25 mono-(ester isopropylique) de PMEHx;
- di-(ester isopropylique) de 6-chloro-9-(2-phosphonylméthoxy)éthylpurine;
- 30 di-(ester isopropylique) de 9-(2-phosphonylméthoxy)éthylpurine;
- mono-(ester isopropylique) de PMEA;
- ester (mono-isopropylique, mono-pivaloyloxyméthylique) de PMEA; ou
- 35 ester (mono-isopropylique, mono-phénylique) de PMEA;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.
13. Procédé selon la revendication 1 ou la revendication 3 pour produire un composé qui est
- 40 di-(ester phénylique) de PMEA;
- di-(ester p-nitrobenzylique) de PMEA;
- 45 di-(ester 2,2,2-trichloroéthylique) de PMEA;
- di-(ester p-trifluorométhylbenzylique) de PMEA;
- 50 mono-(ester cholinique) de PMEA;
- ester (mono-N,N-diéthylacétamidique, mono-pivaloyloxyméthylique) de PMEA;
- mono-(ester 3-hydroxypropylque) de PMEA;
- 55 mono-(3-amino-2,2-diméthylpropylamide) de PMEA;
- mono-(ester N,N-diéthylacétamidique) de PMEA;
- mono-(ester de l'acide acétique) de PMEA;

mono-(ester N,N-diisopropylacétamidique) de PMEA;
mono-(ester p-nitrobenzylique) de PMEA; ou
mono-(ester p-trifluorométhylbenzylique) de PMEA;
mono-(ester phénylique) de PMEA;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

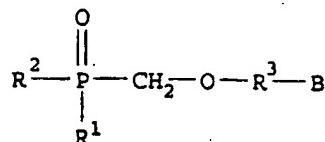
- 10 14. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 13 pour préparer une composition pharmaceutique pour le traitement d'une infection virale chez un mammifère.

15 15. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 13 pour préparer une composition pharmaceutique pour inhiber la croissance d'une tumeur chez un mammifère.

16. Procédé de préparation d'une composition pharmaceutique qui comprend le mélange d'une proportion d'au moins un composé tel que défini dans l'une quelconque des revendications 1 à 13 avec un vecteur ou un excipient sensiblement non toxique pharmaceutiquement acceptable.

20 Revendications pour l'Etat contractant suivant : GR

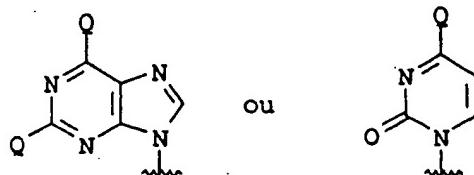
- #### **1. Composé ayant la formule développée I :**



FORMULE

dans laquelle

B représente l'adénine (A), la cytosine (C), la guanine (G), la thymine (T), l'uracile (U), la 2,6-diaminopurine (DAP), l'hypoxanthine (Hx).



dans laquelle

Q est indépendamment choisi parmi H, Cl, NHR⁵, NHR⁵₂, NHC(O)R⁵, N(C(O)R⁵)₂, OH ou NCHN(R⁵)₂.

50 R¹ et R² sont identiques ou différents et représentent indépendamment OR⁴, NH₂, NHR⁵ ou N(R⁵)₂; R¹ et R² étant éventuellement liés l'un à l'autre pour former un groupe cyclique, ou R¹ ou R² étant éventuellement liés à R³ pour former un groupe cyclique;

55 R³ représente un groupe alkylène en C₁ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène; ou R³ représente CH(CH₂OR⁶)CH₂, auquel cas R¹ et R² peuvent en outre représenter indépendamment OH, et R⁶ représente un groupe ester hydrolysable;

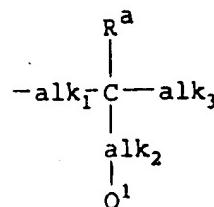
5 R⁴ représente un groupe ester physiologiquement hydrolysable choisi parmi CH₂C(O)NR⁵₂, CH₂C(O)OR⁵, CH₂OC(O)R⁵, CH(R⁵)OC(O)R⁵ (stéréochimie R; S; ou RS), CH₂C(R⁵)₂CH₂OH, ou CH₂OR⁵; ou R⁴ représente un groupe alkyle, arylalkyle ou aryle en C₄ à C₂₀ qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène à condition que R¹ et R² ne représentent pas simultanément le groupe alkoxy;

10 R⁵ représente un groupe alkyle, aryle ou arylalkyle en C₁ à C₂₀ qui peut être substitué ou non substitué par des substituants indépendamment choisis parmi le groupe constitué du groupe hydroxy et du groupe halogène;

15 sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci; à condition que soient exclus les composés de la formule I ci-dessus dans lesquels :

20 B représente l'adénine, la xanthine, l'hypoxanthine, la guanine, la 2-aminopurine, la 2,6-diaminopurine, la cytosine, la thymine, ou l'uracile,

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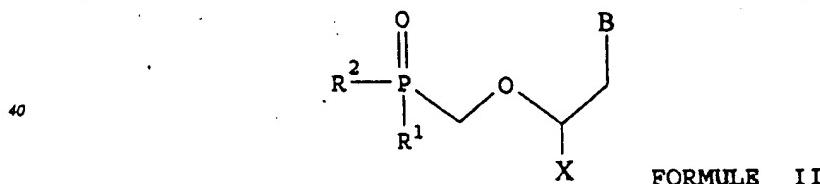


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20 R³ représente où alk₁ est lié à B, alk₁, alk₂ et alk₃ sont indépendamment choisis parmi une liaison chimique ou un groupe alkylène en C₁ à C₄, R⁴ représente l'hydrogène ou un groupe alkyle en C₁ à C₄ et Q¹ représente l'hydrogène ou un groupe hydroxyle, et R¹ et R² représentent des groupes alkoxy en C₄ à C₆, phénoxy ou phényl-(C₁ à C₄)-alkoxy non substitués.

25 2. Composé selon la revendication 1 qui a la formule développée générale II :

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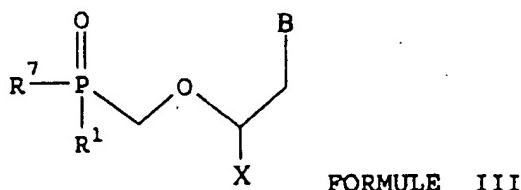
dans laquelle

50 B, R¹ et R² sont tels que décrits dans la revendication 1, à condition que lorsque Q représente NCHN(R⁵)₂, alors R⁵ ne représente pas CH₃;

55 X représente l'hydrogène, CH₂OR⁶ (stéréochimie R; S; ou RS), ou un groupe alkyle inférieur substitué ou non substitué, en particulier le groupe méthyle ou hydroxyméthyle; lorsque X représente CH₂OR⁶, R¹ et R² peuvent en outre être indépendamment choisis parmi OH; et

55 R⁶ représente un groupe ester hydrolysable.

3. Composé ayant la formule développée générale III :



10 dans laquelle

B, et R¹ sont tels que précédemment décrits dans la revendication 1;

15 X représente l'hydrogène, CH₂OR⁶ (stéréochimie R; S; ou RS) ou un groupe alkyle inférieur substitué ou non substitué, en particulier le groupe méthyle ou hydroxyméthyle; lorsque X représente CH₂OR⁶, R¹ peut en outre représenter OH; et R⁶ représente un groupe ester hydrolysable;

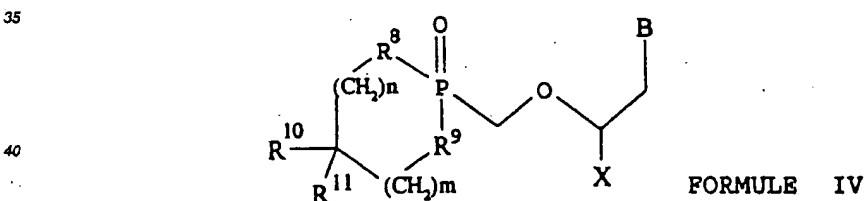
20 R⁷ représente OH, NH₂, NHR⁵, ou NR⁵₂; et

25 R⁵ est tel que décrit dans la revendication 1;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci;
à condition que soient exclus les composés de la formule III ci-dessus dans laquelle :

30 B représente l'adénine, la xanthine, l'hypoxanthine, la guanine, la 2-aminopurine, la 2,6-diaminopurine, la cytosine, la thymine, ou l'uracile,

35 X représente alk₂-Q¹
où alk₂ est choisi parmi une liaison chimique ou un groupe alkylène en C₁ à C₄, Q¹ représente l'hydrogène ou le groupe hydroxyle, et R¹ et R⁷ représentent OH, un groupe alkoxy en C₄ à C₆, phenoxy ou phényl-(C₁ à C₄)-alkoxy non substitué.

4. Composé selon la revendication 1 qui a la formule développée générale IV :



45 dans laquelle

R⁸ et R⁹ sont identiques ou différents et représentent indépendamment NR¹², ou l'oxygène;

50 R¹⁰ et R¹¹ sont identiques ou différents et représentent indépendamment l'hydrogène, ou R⁵,

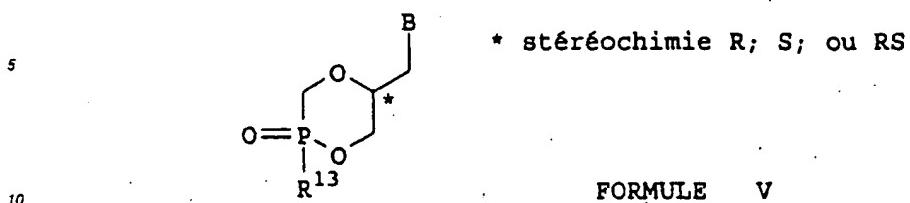
R¹² représente l'hydrogène ou un groupe alkyle inférieur;

m et n sont identiques ou différents et représentent indépendamment 0 ou 1;

55 B et R⁵ sont tels que décrits dans la revendication 1; et

X est tel que décrit dans la revendication 2.

5. Composé qui a la formule développée générale V :



dans laquelle

15 R^{13} représente OR^4 , NHR^5 , NR^5_2 , ou OH , à condition que R^{13} ne représente pas OH lorsque B représente A ou C ; et

20 B , R^4 , et R^5 sont tels que décrits dans la revendication 1;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

25 6. Composé selon la revendication 1, dans lequel R^4 représente un groupe alkyle, aryle ou aryl-alkyle en C_4 à C_{20} qui peut être non substitué ou substitué par des substituants indépendamment choisis parmi les groupes hydroxy et halogène.

30 7. Composé selon la revendication 1 dans lequel R^1 et R^2 représentent OR^4 , et R^4 représente un groupe ester physiologiquement hydrolysable choisi parmi $CH_2OC(O)R^5$ et $CH(R^5)OC(O)R^5$ (stéréochimie R; S; ou RS); ou le groupe aryle dans lequel le groupe aryle est substitué par des substituants indépendamment choisis parmi les groupes hydroxy et halogène.

35 8. Composé selon la revendication 1 qui est

di-(ester propionyloxyméthylique) de PMEA;

di-(ester isobutyryloxyméthylique) de PMEA;

35 bis-diéthylamide de PMEA;

di-(ester acétate de butyle) de PMEA;

40 di-(ester acétate d'éthyle) de PMEA;

di-(ester benzoylexyméthylique) de PMEA;

dibutylamide de PMEA;

45 di-(ester 2-méthylpropylque) de PMEA; ou

di-(ester 3-méthylbutylque) de PMEA.

50 9. Composé selon la revendication 1 qui est

di-(ester pivaloyloxyméthylique) de PMEA.

55 10. Composé selon la revendication 3 qui est

mono-(ester pivaloyloxyméthylique) de PMEA;

mono-(ester octylque) de PMEA;

mono-(ester hydroxy-2,2-diméthylpropylque) de PMEA;
mono-(ester 2,2,2-trichloroéthylique) de PMEA; ou
5 mono-(ester 2,2-difluoro-3-hydroxypropylque) de PMEA.

11. Composé selon la revendication 4 qui est

10 diester cyclopropanylique de PMEA;
diester (2,2-diméthyl)cyclopropanylique de PMEA;
diamide (2,2-diméthyl)cyclopropanylique de PMEA
15 diamide N,N'-diméthyl-cyclopropanylique de PMEA.

12. Composé qui est

20 di-(ester isopropylque) de PMEA;
mono-(ester isopropylque) de PMEHx;
di-(ester isopropylque) de 6-chloro-9-(2-phosphorylméthoxy)éthylpurine;
25 di-(ester isopropylque) de 9-(2-phosphorylméthoxy)éthylpurine;
mono-(ester isopropylque) de PMEA;
ester (mono-isopropylque, mono-pivaloyloxyméthylique) de PMEA; ou
30 ester (mono-isopropylque, mono-phénylique) de PMEA;
sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

13. Composé qui est

35 di-(ester phénylique) de PMEA;
di-(ester p-nitrobenzylique) de PMEA;
40 di-(ester 2,2,2-trichloroéthylique) de PMEA;
di-(ester p-trifluorométhylbenzylique) de PMEA;
mono-(ester cholinique) de PMEA;
45 ester (mono-N,N-diéthylacétamidique, mono-pvaloyloxyméthylique) de PMEA;
mono-(ester 3-hydroxypropylque) de PMEA;
50 mono-(3-amino-2,2-diméthylpropylamide)) de PMEA;
mono-(ester N,N-diéthylacétamidique) de PMEA;
mono-(ester de l'acide acétique) de PMEA;
55 mono-(ester N,N-diisopropylacétamidique) de PMEA;
mono-(ester p-nitrobenzylique) de PMEA; ou

mono-(ester p-trifluorométhylbenzyllique) de PMEA;

mono-(ester phénylique) de PMEA;

sels d'addition d'acide, sels de métal, et solvates pharmaceutiquement acceptables de celui-ci.

- 5 14. Procédé de production du composé selon la revendication 1, 2, 12 ou 13 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'alkylation du phosphonate avec l'halogénure d'alkyle approprié; ou l'hydrolyse des diéthers ou des diamines.
- 10 15. Procédé de production du composé selon la revendication 3, 12 ou 13 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'hydrolyse des diéthers ou des diamines.
- 15 16. Procédé de production du composé selon la revendication 4 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié.
- 20 17. Procédé de production du composé selon la revendication 5 qui comprend la réaction du phosphonate avec un agent activant, puis la réaction avec l'amine ou l'alcool approprié; ou l'alkylation du phosphonate avec l'halogénure d'alkyle approprié.
- 25 18. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 13 pour préparer une composition pharmaceutique pour le traitement d'une infection virale chez un mammifère.
- 30 19. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 13 pour préparer une composition pharmaceutique pour inhiber la croissance d'une tumeur chez un mammifère.
- 35 20. Procédé de préparation d'une composition pharmaceutique qui comprend le mélange d'une proportion d'au moins un composé tel que défini dans l'une quelconque des revendications 1 à 13 avec un vecteur ou un excipient sensiblement non toxique pharmaceutiquement acceptable.

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